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(54) **PROCESS AND INTERMEDIATES FOR THE PRODUCTION OF CCR2 ANTAGONISTS**

(71) Applicants: **Heiner Ebel**, Biderach an der Riss (DE); **Sara Frattini**, Castelleone (IT); **Riccardo Giovannini**, Verona (IT); **Christoph Hoenke**, Biberach an der Riss (DE); **Thomas Trieselmann**, Mettenberg (DE); **Patrick Tielmann**, Bad Soden am Taunus (DE)

(72) Inventors: **Heiner Ebel**, Biderach an der Riss (DE); **Sara Frattini**, Castelleone (IT); **Riccardo Giovannini**, Verona (IT); **Christoph Hoenke**, Biberach an der Riss (DE); **Thomas Trieselmann**, Mettenberg (DE); **Patrick Tielmann**, Bad Soden am Taunus (DE)

(73) Assignee: **Boehringer Ingelheim International GmbH**, Ingelheim am Rhein (DE)

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Primary Examiner — Alexander R Pagano

(74) *Attorney, Agent, or Firm* — Michael P. Morris; Edward S. Lazer

(57) **ABSTRACT**

The present invention relates to a process for the production of novel antagonists for CCR2 (CC chemokine receptor 2) and intermediates thereof.

9 Claims, No Drawings

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PROCESS AND INTERMEDIATES FOR THE PRODUCTION OF CCR2 ANTAGONISTS

FIELD OF INVENTION

The present invention relates to novel antagonists for CCR2 (CC chemokine receptor 2) and their use for providing medicaments for treating conditions and diseases where activation of CCR2 plays a causative role, especially pulmonary diseases like asthma and COPD, neurologic disease, especially of pain diseases, immune related diseases, especially diabetes mellitus including diabetes nephropathy, and cardiovascular diseases, especially atherosclerotic disease.

BACKGROUND OF THE INVENTION

The chemokines are a family of small, proinflammatory cytokines, with potent chemotactic activities. Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract various cells, such as monocytes, macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation.

Chemokine receptors, such as CCR2 or CCR5 have been implicated as being important mediators of inflammatory and immunoregulatory disorders and diseases as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. Accordingly, agents which modulate chemokine receptors such as the CCR2 and CCR5 receptor would be useful in such disorders and diseases.

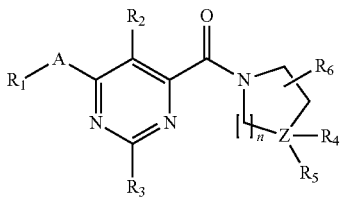
In particular it is widely accepted that numerous conditions and diseases involve inflammatory processes. Such inflammations are critically triggered and/or promoted by the activity of macrophages, which are formed by differentiation out of monocytes. It has further been found that monocytes are characterized by, e.g., a high expression of membrane-resident CCR2, whereas the CCR2 expression in macrophages is lower. CCR2 is a critical regulator of monocytes trafficking, which can be described as the movement of the monocytes towards an inflammation along a gradient of monocyte chemoattractant proteins (MCP-1, MCP-2, MCP-3, MCP-4).

Therefore, in order to reduce macrophage-induced inflammation, it would be desirable to block the monocyte CCR2 by an antagonist, so that the monocytes can be less triggered to move towards an inflammation area for conversion into macrophages.

Based on the aforesaid there is a need for providing effective antagonists for CCR2, which are pharmacologically acceptable.

DESCRIPTION OF THE INVENTION

It has now been found that such effective CCR2 inhibitors can be provided by compounds according to general formula (I),



(I)

wherein R_1 is $-L_1-R_7$,

wherein L_1 is a linker selected from a bond or a group selected from $—C_1-C_2$-alkylene, and $—C_1-C_2$-alkenylene which optionally comprises one or more groups selected from —O—, —C(O)—, and —NH— in the chain and which is optionally substituted by a group selected from among —OH, $—NH_2$, $—C_1-C_3$-alkyl, $O—C_1-C_6$-alkyl, and —CN,

wherein R_7 is a ring selected from among $—C_3-C_8$-cycloalkyl, $—C_3-C_8$-heterocyclyl, $—C_5-C_{10}$-aryl, and $—C_5-C_{10}$-heteroaryl,

wherein the ring R_7 is optionally substituted with one or more groups selected from among $—CF_3$, $—O—CF_3$, —CN, and -halogen,

or wherein the ring R_7 is optionally substituted with one or more groups selected from among $—C_1-C_6$-alkyl, $—O—C_1-C_6$-alkyl, $—C_5-C_{10}$-aryl, $—C_5-C_{10}$-heteroaryl, $—C_3-C_8$-cycloalkyl, $—C_3-C_8$-heterocyclyl, $—C_1-C_6$-alkenyl, and $—C_1-C_6$-alkynyl, optionally being further substituted by one or more groups selected from —OH, $—NH_2$, $—C_1-C_3$-alkyl, $—O—C_1-C_6$-alkyl, —CN, $—CF_3$, $—OCF_3$, halogen, and =O,

or wherein the ring R_7 is optionally further bi-valently substituted on two neighbouring ring atoms, such that an annellated ring is formed by one or more groups selected from among $—C_1-C_6$-alkylene, $—C_2-C_6$-alkenylene and $—C_4-C_6$-alkynylene, in which one or two carbon centers may optionally by replaced by 1 or 2 hetero atoms selected from N, O and S, the bivalent group being optionally substituted by one or more groups selected from —OH, $—NH_2$, $—C_1-C_3$-alkyl, $—O—C_1-C_6$-alkyl, —CN, $—CF_3$, $—OCF_3$, halogen, and =O;

R_2 is selected from among —H, -halogen, —CN, $—O—C_1-C_4$-alkyl, $—C_1-C_4$-alkyl, $—CH=CH_2$, $—C\equiv CH$, $—CF_3$, $—OCF_3$, $—OCF_2H$, and $—OCFH_2$;

R_3 is selected from among —H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, $—OCH_3$, and —CN;

R_4 and R_5 are independently selected from among an electron pair, —H, $—C_1-C_6$-alkyl, $—NH_2$, $—C_3-C_8$-cycloalkyl, $—C_3-C_8$-heterocyclyl, $—C_5-C_{10}$-aryl, $—C_5-C_{10}$-heteroaryl, and $—C(O)—N(R_8,R_{8'})$,

with R_8 and $R_{8'}$ independently being selected from among —H and $—C_1-C_6$-alkyl, wherein R_4 and R_5 if different from an electron pair or —H are optionally independently substituted with one or more groups selected from among -halogen, —OH, $—CF_3$, —CN, $—C_1-C_6$-alkyl, $—O—C_1-C_6$-alkyl, $—O—C_3-C_8$-cycloalkyl, $—O—C_3-C_8$-heterocyclyl, $—O—C_5-C_{10}$-aryl, $—O—C_5-C_{10}$-heteroaryl, $—C_0-C_6$-alkylene-CN, $—C_0-C_4$-alkylene-$O—C_1-C_4$-alkyl, $—C_0-C_4$-alkylene-$O—C_3-C_8$-cycloalkyl, $—C_0-C_4$-alkylene-$O—C_3-C_8$-heterocyclyl, $—C_0-C_4$-alkylene-$O—C_5-C_{10}$-aryl, $—C_0-C_4$-alkylene-$O—C_5-C_{10}$-heteroaryl, $—C_0-C_4$-alkylene-$Q-C_0-C_4$-alkyl-$N(R_9,R_{9'})$, $—C_0-C_4$-alkylene-$N(R_{10})-Q-C_1-C_4$-alkyl, $—C_0-C_4$-alkylene-$N(R_{10})-Q-C_3-C_8$-cycloalkyl, $—C_0-C_4$-alkylene-$N(R_{10})-Q-C_3-C_8$-heterocyclyl, $—C_0-C_4$-alkylene-$N(R_{10})-Q-C_5-C_{10}$-aryl, $—C_0-C_4$-alkylene-$N(R_{10})-Q-C_5-C_{10}$-heteroaryl, $—C_0-C_4$-alkylene-$Q-N(R_{11},R_{11'})$, $—C_0-C_4$-alkylen-$N(R_{12})-Q-N(R_{13},R_{13'})$, $—C_0-C_4$-alkylen-R_{14}, $—C_0-C_4$-alkylene-$Q-C_1-C_6$-alkyl, $—C_0-C_4$-alkylene-$Q-C_3-C_8$-cycloalkyl, $—C_0-C_4$-alkylene-$Q-C_3-C_8$-heterocyclyl, $—C_0-C_4$-alkylene-$Q-C_5-C_{10}$-aryl, $—C_0-C_4$-alkylene-$Q-C_5-C_{10}$-heteroaryl, $—C_0-C_4$-alkylene-$O-Q-N(R_{15},R_{15'})$, and $—C_0-C_4$-alkylene-$N(R_{16})-Q-O—(R_{17})$

wherein Q is selected from among —C(O)— and $—SO_2—$

wherein R_{12}, R_{16}, are independently selected from among —H, $—C_1-C_6$-alkyl, and $—C_3-C_6$-cycloalkyl,

wherein R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$, R_{13}, $R_{13'}$, R_{15}, $R_{15'}$ are independently selected from among —H and $—C_1-C_6$-alkyl, and $—C_3-C_6$-cycloalkyl,

or wherein R_9 and $R_{9'}$, R_{11} and $R_{11'}$, R_{13} and $R_{13'}$, R_{15} and $R_{15'}$, together form a —C_2-C_6-alkylene group, preferably a —C_5-C_6-alkylene group,

wherein R_{14} and R_{17} are independently selected from among —H, —C_1-C_6-alkyl, —C_5-C_{10}-aryl, —C_5-C_{10}-heteroaryl, —C_3-C_8-cycloalkyl, and —C_3-C_8-heterocyclyl, wherein said —C_3-C_8-heterocyclyl optionally comprises nitrogen and/or —SO_2— in the ring, and wherein R_{14} and R_{17} are optionally substituted with one or more groups selected from among —OH, —OCH_3, —CF_3, —OCF_3, —CN, -halogen, —C_1-C_4-alkyl, =O, and —SO_2—C_1-C_4-alkyl,

or wherein R_4 and/or R_5 are independently a group of the structure -L_2-R_{18},

wherein L_2 is selected from among —NH—, and —N(C_1-C_4-alkyl)-,

wherein R_{18} is selected from among —C_5-C_{10}-aryl, —C_5-C_{10}-heteroaryl, —C_3-C_8-cycloalkyl, and —C_3-C_8-heterocyclyl,

wherein R_{18} is optionally substituted by one or more groups selected from among halogen, —CF_3, —OCF_3, —CN, —OH, —O—C_1-C_4-alkyl, —C_1-C_6-alkyl, —NH—C(O)—C_1-C_6-alkyl, —N(C_1-C_4-alkyl)-C(O)—C_1-C_6-alkyl, —C(O)—C_1-C_6-alkyl, —S(O)$_2$—C_1-C_6-alkyl, —NH—S(O)$_2$—C_1-C_6-alkyl, —N(C_1-C_4-alkyl)-S(O)$_2$—C_1-C_6-alkyl, and —C(O)—O—C_1-C_6-alkyl,

and wherein R_4, R_5 and R_{18} are optionally further substituted by spiro-C_3-C_8-cycloalkyl or spiro-C_3-C_8-heterocyclyl such that together with R_4, R_5 and/or R_{18} a spirocycle is formed, wherein said spiro-C_3-C_8-heterocyclyl optionally comprises one or more groups selected from among nitrogen, —C(O)—, —SO_2—, and —N(SO_2—C_1-C_4-alkyl)- in the ring,

or wherein R_4, R_5 and R_{18} are optionally further bi-valently substituted by one or more spirocyclic or annellated ring forming groups selected from among —C_1-C_6-alkylene, —C_2-C_6-alkenylene, and —C_4-C_6-alkynylene, in which one ore two carbon centers may optionally be replaced by one or two hetero atoms selected from among N, O and S and which may optionally be substituted by one or more groups on one ring atom or on two neighbouring ring atoms selected from among —OH, —NH_2, —C_1-C_3-alkyl, 0-C_1-C_6-alkyl, —CN, —CF_3, —OCF_3, and halogen;

R_6 is selected from among —H, —C_1-C_4-alkyl, —OH, —O—C_1-C_4-alkyl, -halogen, —CN, —CF_3, and —OCF_3;

A is selected from among a single bond, =CH—, —CH_2—, —O—, —S—, and —NH—;

n is 1, 2 or 3;

Z is C or N,

as well as in form of their acid addition salts with pharmacologically acceptable acids, as well as in form of their solvates and/or hydrates.

Preferred compounds of formula (I) according to the invention are compounds with R_2, R_3, R_4, R_5, R_6, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$, R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, A, L_2, Z, Q, and n as herein before or below defined, wherein R_1 is -L_1-R_7,

with L_1 being a linker selected from a bond or a group selected from among —C_1-C_2-alkylene, and —C_1-C_2-alkenylene optionally comprising one or more groups selected from among —O—, —C(O)—, and, —NH— in the chain and optionally being substituted by a group selected from among —OH, —NH_2, —C_1-C_3-alkyl, 0-C_1-C_6-alkyl, and —CN,

wherein R_7 is a ring selected from among —C_3-C_8-cycloalkyl, —C_5-C_{10}-aryl, —C_3-C_8-heterocyclyl comprising 1 or 2 hetero atoms selected from among N, and O, and —C_5-C_{10}-heteroaryl comprising 1 or 2 hetero atoms selected from among N, and O,

wherein the ring R_7 is optionally substituted with one or more groups selected from among —CF_3, —O—CF_3, —CN, and -halogen,

or wherein the ring R_7 is optionally substituted with one or more groups selected from among —C_1-C_6-alkyl, —O—C_1-C_6-alkyl, —C_5-C_{10}-aryl, —C_3-C_8-cycloalkyl, —C_3-C_8-heterocyclyl, —C_1-C_6-alkenyl, and —C_1-C_6-alkynyl, optionally being substituted by one or more groups selected from —OH, —NH_2, —C_1-C_3-alkyl, —O—C_1-C_6-alkyl, —CN, —CF_3, —OCF_3, halogen, and =O,

or wherein the ring R_7 is optionally further bi-valently substituted by one or more annellated ring forming groups selected from among —C_1-C_6-alkylene, —C_2-C_6-alkenylene and —C_4-C_6-alkynylene, in which one or two carbon centers may optionally by replaced by 1 or 2 hetero atoms selected from N, and O, wherein the bivalent group is optionally substituted by one or more groups selected from —OH, —NH_2, —C_1-C_3-alkyl, —O—C_1-C_6-alkyl, —CN, —CF_3, —OCF_3, halogen, and =O;

Preferred compounds of formula (I) according to the invention are compounds with R_2, R_3, R_4, R_5, R_6, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$, R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, A, L_2, Z, Q, and n as herein before or below defined, wherein R_1 is -L_1-R_7,

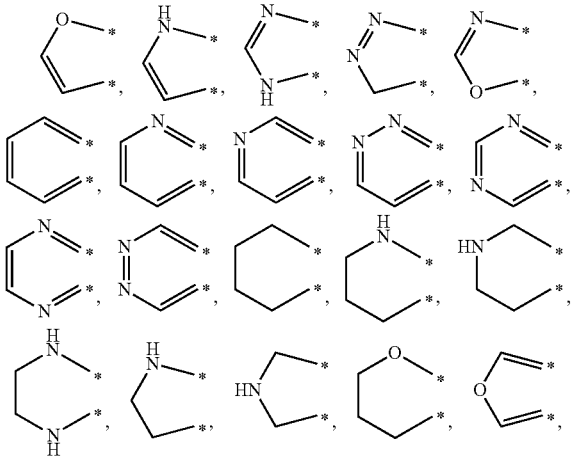
wherein L_1 is a linker selected from among a bond, methylene, ethylene, methenylene, and ethenylene,

wherein L_1, if different from a bond, is optionally substituted with one or more groups selected from among methyl, and ethyl,

wherein R_7 is a ring selected from among cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, pyrrolidinyl, piperidinyl, azepanyl, tetrahydrofuranyl, tetrahydropyranyl, oxepanyl, phenyl, pyridyl, and furanyl,

wherein the ring R_7 is optionally substituted with one or more groups selected from among —F, —Cl, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, -t-butyl, —CF_3, —O—CF_3, —CN, —O-methyl, -furanyl and -phenyl, wherein said furanyl and said phenyl are optionally independently substituted by one or more groups selected from among —C_1-C_6-alkyl, or halogen, —OCH_3, —CF_3, and —OCF_3.

or wherein R_7 is bi-valently substituted by one or more groups selected from among



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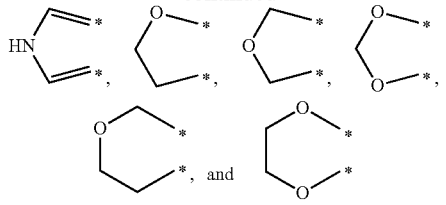
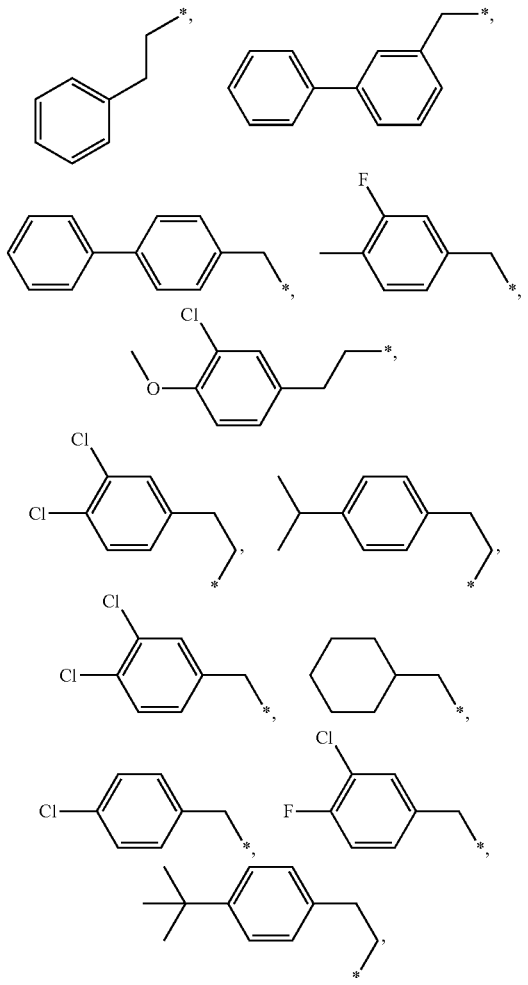


on two neighbouring ring atoms, such that an annellated ring is formed.

Preferred compounds of formula (I) according to the invention are compounds with R_2, R_3, R_4, R_5, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$, R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$ R_{16}, R_{17}, R_{18}, A, L_2, Z, Q, and n as herein before or below defined, wherein R_1 is -L_1-R_7,

and wherein L_1 is a linker selected from among a bond, methylene, ethylene, methenylene, and ethenylene and wherein L_1 is optionally substituted with one or more of methyl or ethyl and wherein L_1 optionally comprises one or more —O— atoms.

Preferred compounds of formula (I) according to the invention are compounds with R_2, R_3, R_4, R_5, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$, R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$ R_{16}, R_{17}, R_{18}, A, L_2, Z, Q, and n as herein before or below defined, wherein R_1 is selected from among



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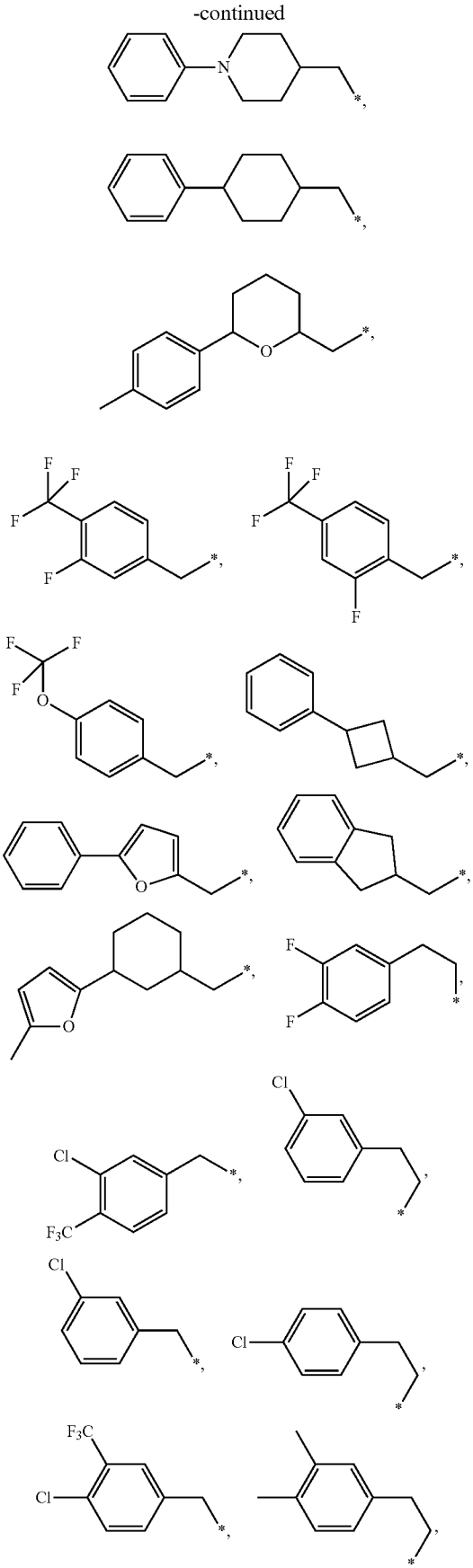

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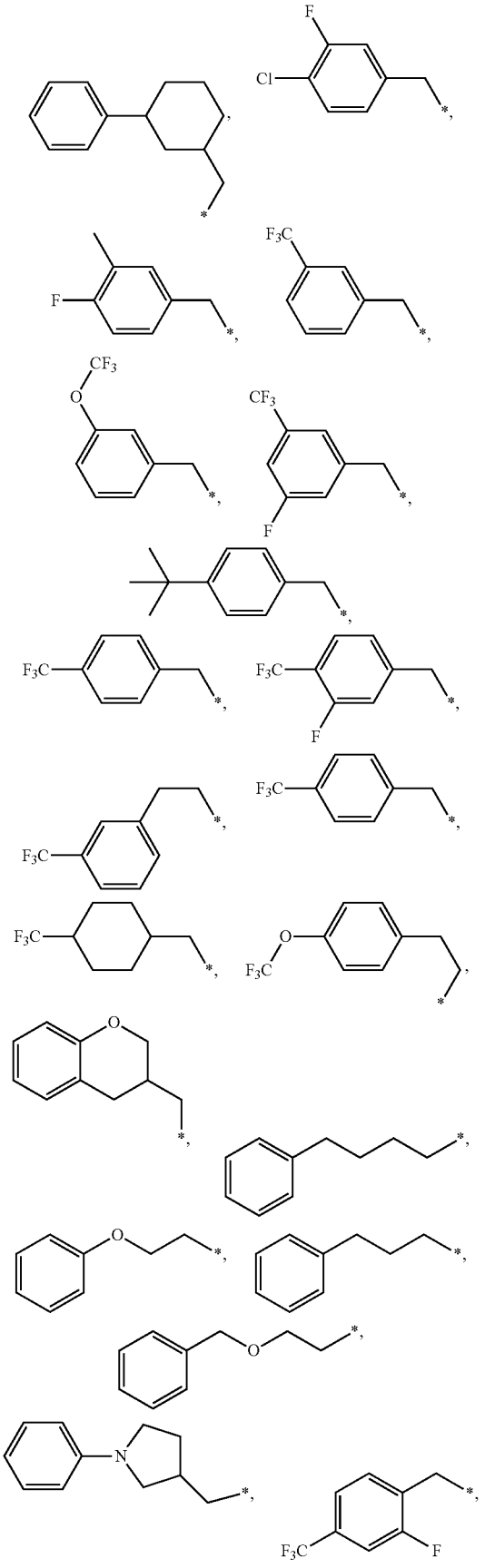

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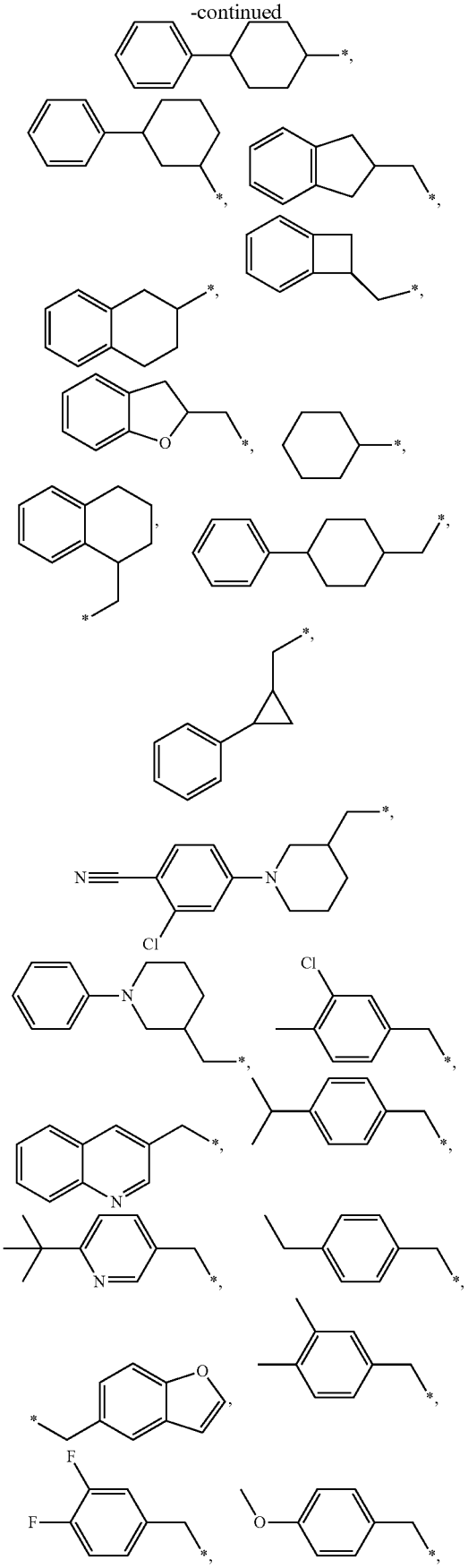

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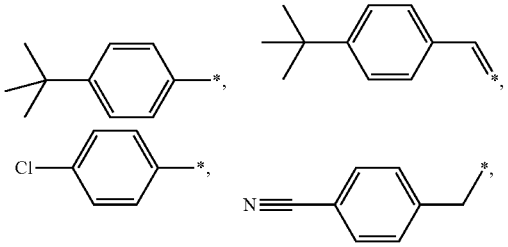

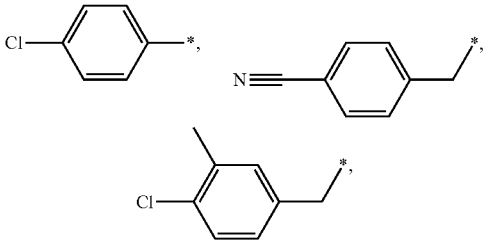

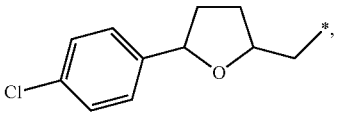

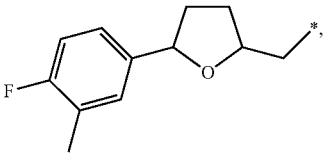

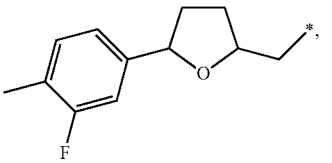

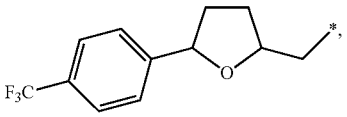

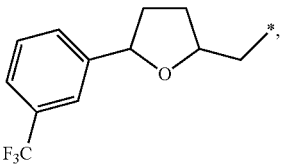

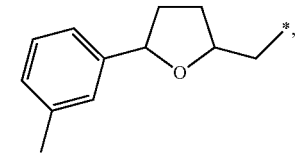

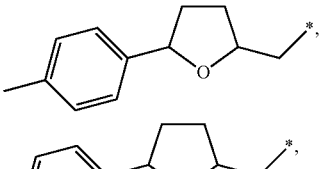

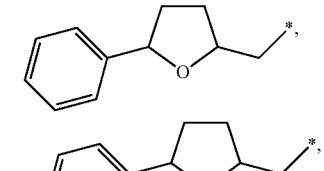

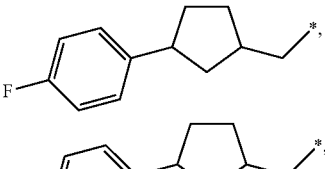

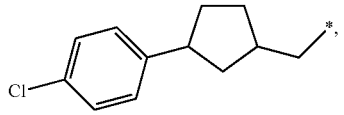

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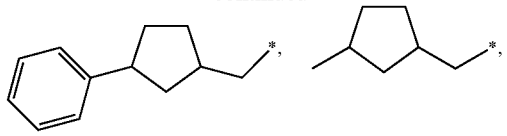

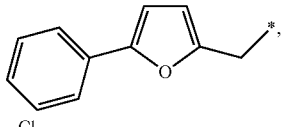

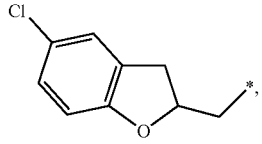

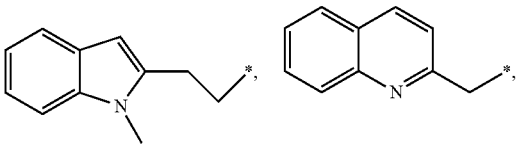

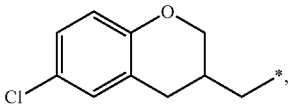

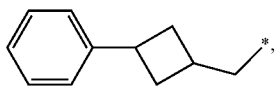

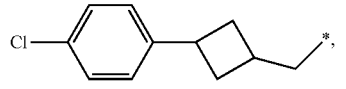

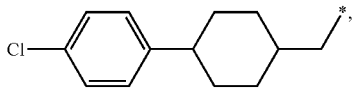

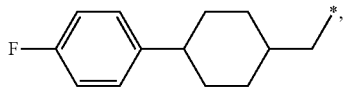

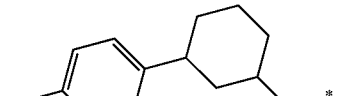

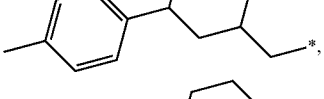

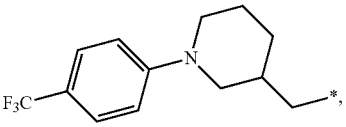

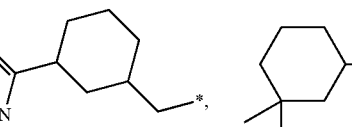

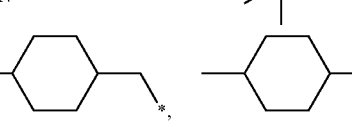

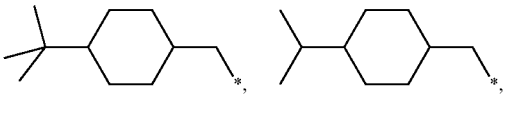

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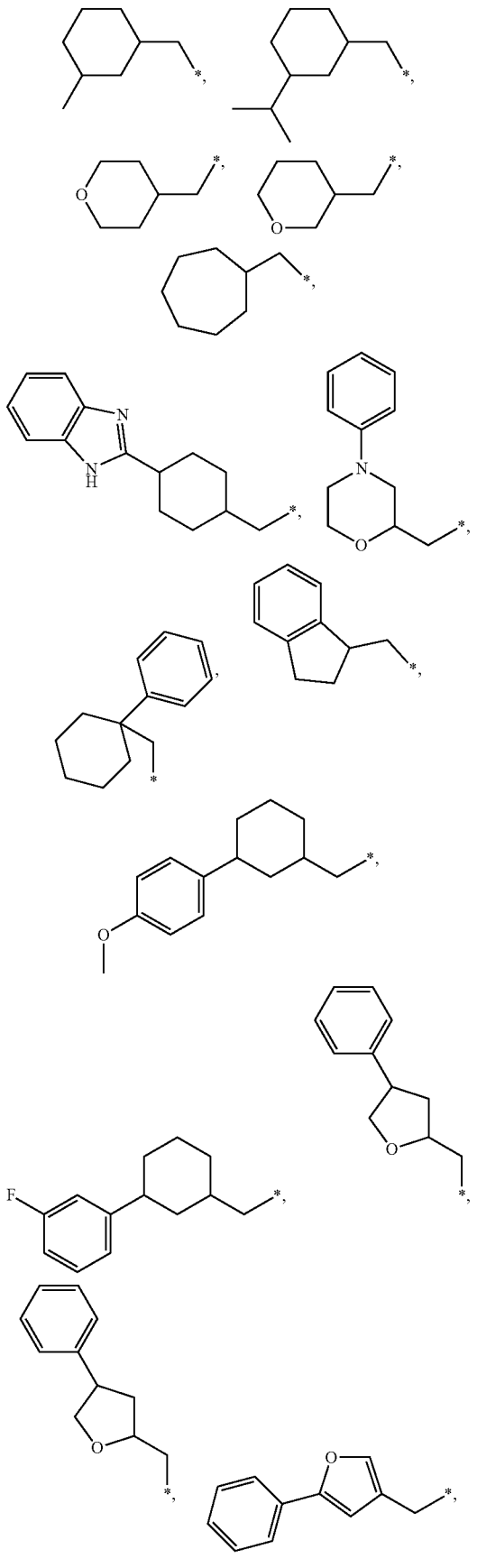

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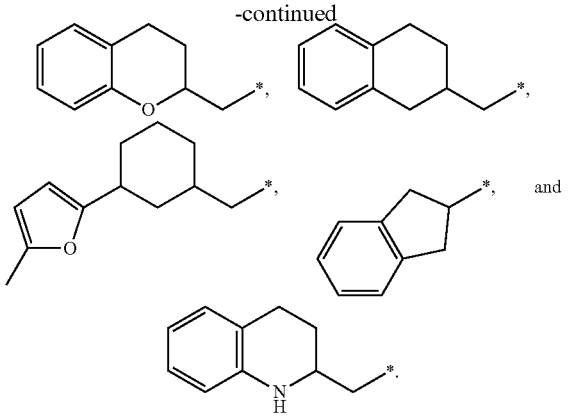


and

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_3, R_4, R_5, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$, R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, A, L_1, L_2, Z, Q, and n as herein before or below defined, wherein R_2 is selected from among —H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, -butyl, -i-butyl, -t-butyl, —F, —Cl, —Br, —I, —CN, —CH═CH_2, —C≡CH, and —OCH_3, more preferred from among H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, and —OCH_3.

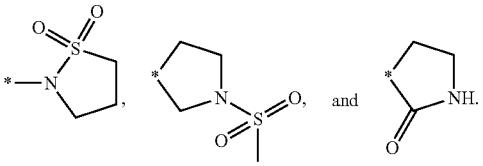
Preferred compounds of formula (I) according to the invention are compounds with R_1, R_3, R_4, R_5, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$, R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, A, L_1, L_2, Z, Q, and n as herein before or below defined, wherein R_2 is selected from among —H, -Methyl, -Ethyl, —Br, and —OCH_3.

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_4, R_5, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$, R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, A, L_1, L_2, Z, Q, and n as herein before or below defined, wherein R_3 is selected from among —H, and -methyl.

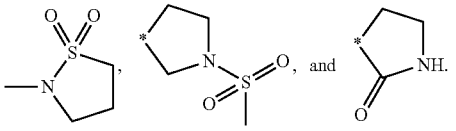
Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_6, R_7, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$, R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, A, L_1, L_2, Z, Q, and n as herein before or below defined, wherein R_4 and R_5 are independently selected from among an electron pair, —H, -i-propyl, -amino, -pyrrolidinyl, -piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidinyl, -tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and —C(O)—N(R_8, $R_{8'}$), with R_8 and $R_{8'}$ independently being selected from among —H and —C_1-C_6-alkyl,

wherein R_4 and R_5 are optionally independently substituted with one or more groups selected from among -fluoro, -methyl, -ethyl, propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -hydroxy, —CF_3, —OCF_3, —CN, —O—CH_3, —O—C_2H_5, —O—C_3H_7, —CH_2—CN, —CH_2—O—CH_3, —$(CH_2)_2$—O—CH_3, —C(O)—CH_3, —C(O)—C_2H_5, —C(O)—C_3H_7, —COOH, —C(O)—NH_2, —C(O)—NH—CH_3, —C(O)—N$(CH_3)_2$, —NH—C(O)—CH_3, —N(CH_3)C(O)—CH_3, —NH—C(O)—C_2H_5, —N(CH_3)—C(O)—C_2H_5, —NH—C(O)—C_3H_7, —N(CH_3)—C(O)—C_3H_7, —NH—SO_2—CH_3, —N(CH_3)—SO_2—CH_3, —N(C_2H_5)—SO_2—CH_3, —N(C_3H_7)—SO_2—CH_3, —NH—SO_2—C_2H_5, —N(CH_3)—SO_2—C_2H_5, —N(C_2H_5)—SO_2—C_2H_5, —N(C_3H_7)—SO_2—C_2H_5, —NH—SO_2—C_3H_7, —N(CH_3)—SO_2—C_3H_7, —N(C_2H_5)—SO_2—C_3H_7, —N(C_3H_7)—SO_2—C_3H_7, —NH—SO_2—C_3H_5, —N(CH_3)—SO_2—C_3H_5, —N(C_2H_5)—SO_2—C_3H_5, —N(C_3H_7)—SO_2—C_2H_5, —CH_2—NH—SO_2—CH_3, —CH_2—N(CH_3)—SO_2—CH_3, —CH_2—NH—SO_2—

C_2H_5, —CH_2—$N(CH_3)$—SO_2—C_2H_5, —CH_2—NH—SO_2—C_3H_7, —CH_2—$N(CH_3)$—SO_2—C_3H_7, —CH_2—NH—SO_2—C_3H_5, —CH_2—$N(CH_3)$—SO_2—C_3H_5, —NH—C(O)—NH_2, —$N(CH_3)$—C(O)—NH_2, —NH—C(O)—NH—CH_3, —$N(CH_3)$—C(O)—NH—CH_3, —NH—C(O)—$N(CH_3)_2$, —$N(CH_3)$—C(O)—$N(CH_3)_2$, —SO_2—NH_2, —SO_2—$NH(CH_3)$, —SO_2—$N(CH_3)_2$, —C(O)—NH—C_2H_5, —C(O)—$N(CH_3)$—C_2H_5, —C(O)—$N(CH_3)$—C_3H_7, —C(O)—$N(CH_3)$—C_4H_9, —C(O)—NH—$CH(CH_3)$—C_2H_5, —C(O)—$N(CH_3)$—$CH(CH_3)$—C_2H_5, —CH_2—C(O)—NH_2, —CH_2—C(O)—NH—CH_3, —CH_2—C(O)—$N(CH_3)_2$, —$N(CH_3)$—SO_2—$N(CH_3)_2$, -phenyl, -pyridin-4-yl, —CH_2-3-methyl-oxetan-3-yl, —O-1,2-difluoro-phen-5-yl, —O-pyridin-2-yl, -pyrrolidine-2-one-1-yl, -3,5-dimethyl-[1,2,4]triazol-4-yl, -3-methyl-[1,2,4]oxadiazol-5-yl,

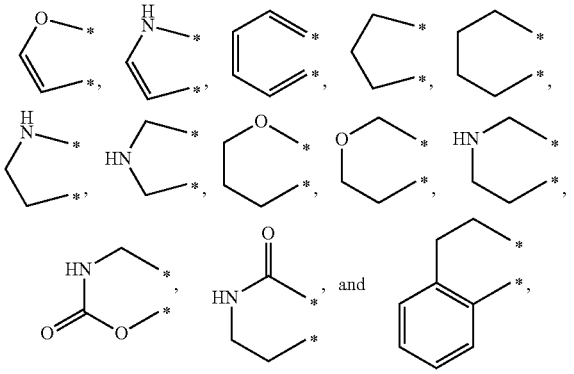


Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$, R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, A, L_1, L_2, Z, Q, and n as herein before or below defined, wherein R_4 and R_5 are independently selected from among an electron pair, —H, -amino, -piperidinyl, -tetrahydropyranyl, and -pyrrolidinyl, wherein R_4 and R_5 are optionally independently substituted with one or more groups selected from among -fluoro, —CF_3, -hydroxy, —O—CH_3, —OCF_3, —CN, —NH—SO_2—CH_3, —$N(CH_3)$—SO_2—CH_3, —$N(C_2H_5)$—SO_2—CH_3, —$N(C_3H_7)$—SO_2—CH_3, —NH—SO_2—C_2H_5, —$N(CH_3)$—SO_2—C_2H_5, —$N(C_2H_5)$—SO_2—C_2H_5, —$N(C_3H_7)$—SO_2—C_2H_5, —NH—SO_2—C_3H_7, —$N(CH_3)$—SO_2—C_3H_7, —$N(C_2H_5)$—SO_2—C_3H_7, —$N(C_3H_7)$—SO_2—C_3H_7, —NH—SO_2—C_3H_5, —$N(CH_3)$—SO_2—C_3H_5, —$N(C_2H_5)$—SO_2—C_3H_5, —$N(C_3H_7)$—SO_2—C_2H_5, —CH_2—NH—SO_2—CH_3, —CH_2—$N(CH_3)$—SO_2—CH_3, —CH_2—NH—SO_2—C_2H_5, —CH_2—$N(CH_3)$—SO_2—C_2H_5, —CH_2—NH—SO_2—C_3H_7, —CH_2—$N(CH_3)$—SO_2—C_3H_7, —CH_2—NH—SO_2—C_3H_5, —CH_2—$N(CH_3)$—SO_2—C_3H_5, —NH—C(O)—NH_2, —$N(CH_3)$—C(O)—NH_2, —NH—C(O)—NH—CH_3, —$N(CH_3)$—C(O)—NH—CH_3, —NH—C(O)—$N(CH_3)_2$, —$N(CH_3)$—C(O)—$N(CH_3)_2$, —SO_2—NH_2, —SO_2—$NH(CH_3)$, —SO_2—$N(CH_3)_2$, —C(O)—NH—C_2H_5, —C(O)—$N(CH_3)$—C_2H_5, —C(O)—$N(CH_3)$—C_3H_7, —C(O)—$N(CH_3)$—C_4H_9, —C(O)—NH—$CH(CH_3)$—C_2H_5, —C(O)—$N(CH_3)$—$CH(CH_3)$—C_2H_5, —CH_2—C(O)—NH_2, —CH_2—C(O)—NH—CH_3, —CH_2—C(O)—$N(CH_3)_2$, —$N(CH_3)$—SO_2—$N(CH_3)_2$, -pyridin-4-yl, —CH_2-3-methyl-oxetan-3-yl, —O-1,2-difluoro-phen-5-yl, —O-pyridin-2-yl, -pyrrolidine-2-one-1-yl, -3,5-dimethyl-[1,2,4]triazol-4-yl, -3-methyl-[1,2,4]oxadiazol-5-yl,



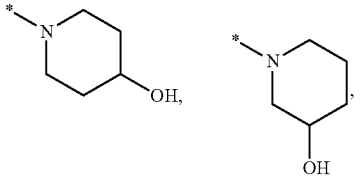
Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$, R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, A, L_1, Z, Q, and n as herein before or below defined, wherein R_4 and R_5 are independently a group of the structure -L_2-R_{18}, wherein L_2 is selected from among —NH—, —$N(CH_3)$— and —$N(C_2H_5)$—, wherein R_{18} is selected from among -tetrahydropyranyl, -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl, -cyclooctyl, -pyrrolidinyl, -piperidinyl, -piperazinyl, -morpholinyl, -chromanyl, -octahydro-pyrano-pyrrolyl, -octahydro-pyrano-pyridinyl, -octahydro-pyrano-oxazinyl, -oxaspirodecanyl, and -tetrahydro-naphthyridinyl, wherein R_{18} is optionally substituted by one or more groups selected from among —F, —CF_3, —OCF_3, —CN, —OH, —O—CH_3, —CH_3, —NH—C(O)—CH_3, —$N(CH_3)$—C(O)—CH_3, —C(O)—CH_3, —$S(O)_2$—CH_3, —NH—$S(O)_2$—CH_3, —$N(CH_3)$—$S(O)_2$—CH_3, and —C(O)—O—C_2H_5.

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$, R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, A, L_1, L_2, Z, Q, and n as herein before or below defined, wherein R_4, R_5 and R_{18} are optionally further bi-valently substituted by one or more groups selected from among



on one ring atom or on two neighboring ring atoms, such that spirocyclic or annellated rings are formed.

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_5, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$, R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, A, L_1, L_2, Z, Q, and n as herein before or below defined, wherein R_4 is selected from among



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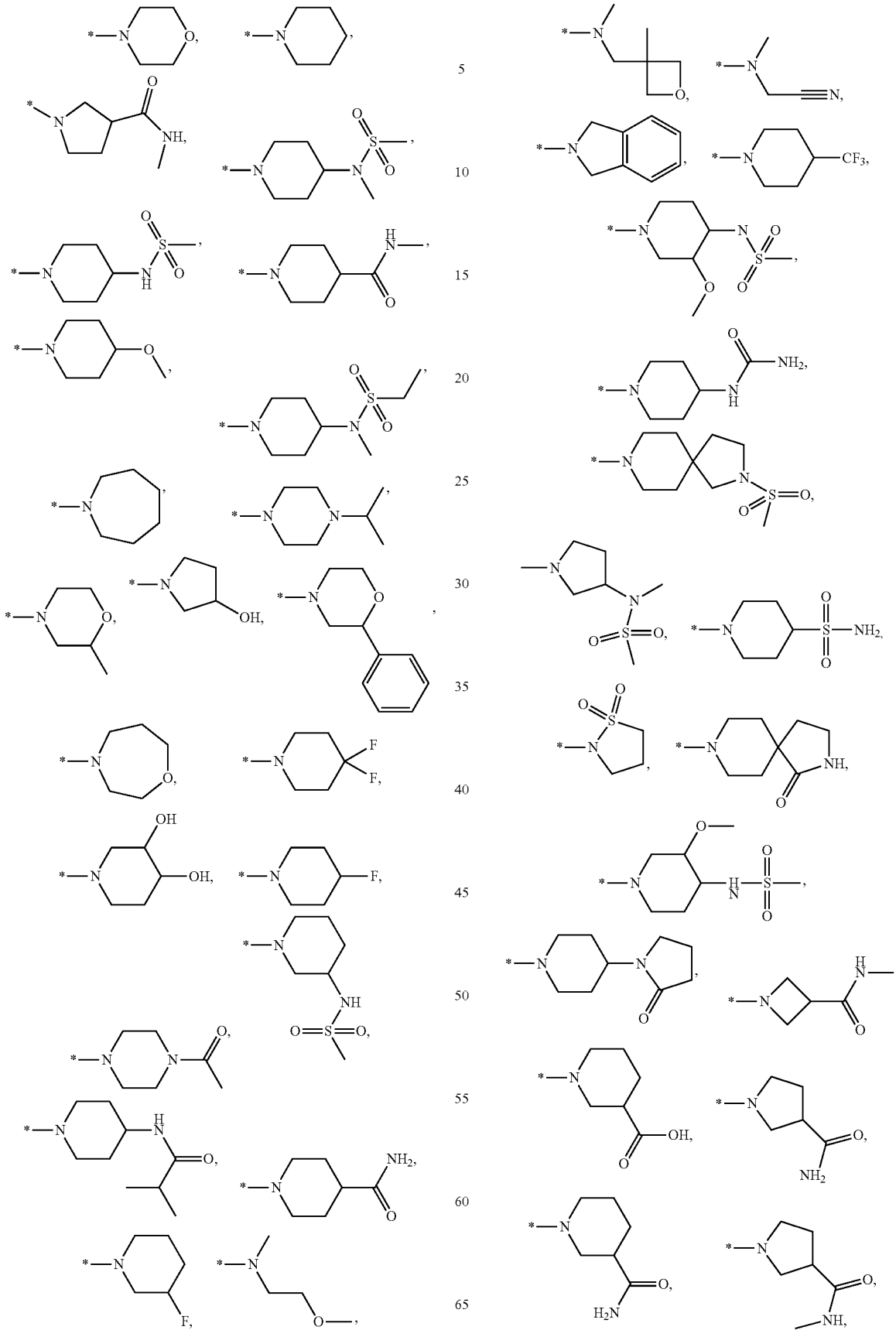

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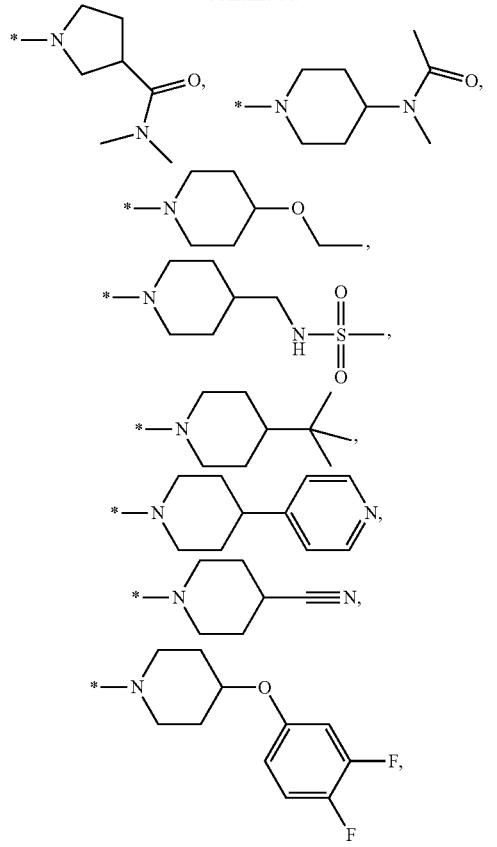

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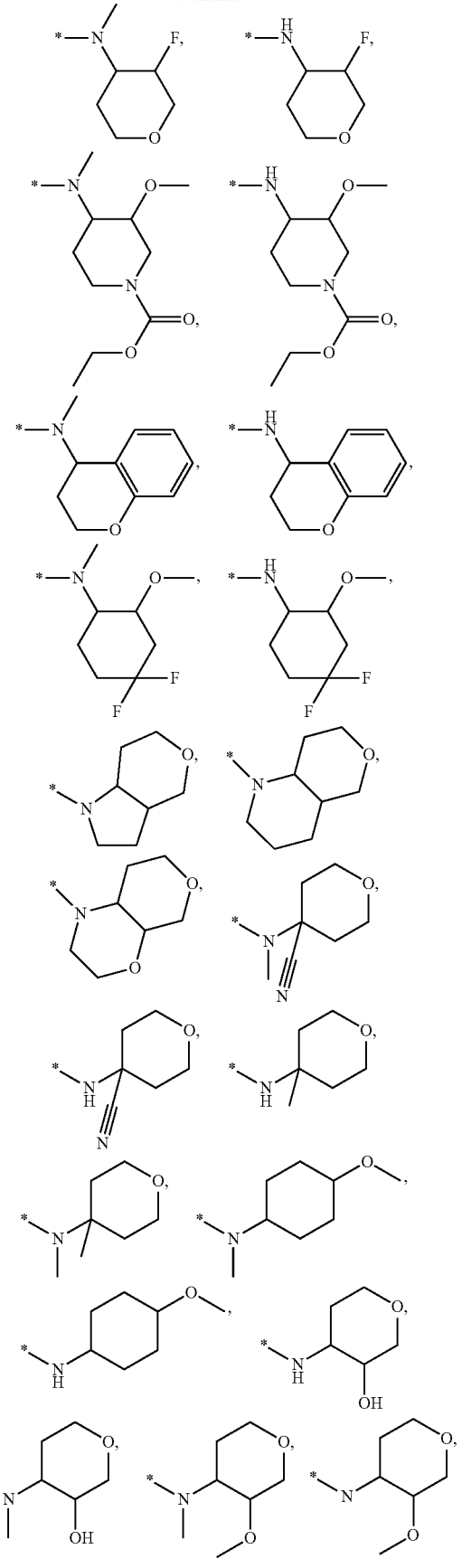

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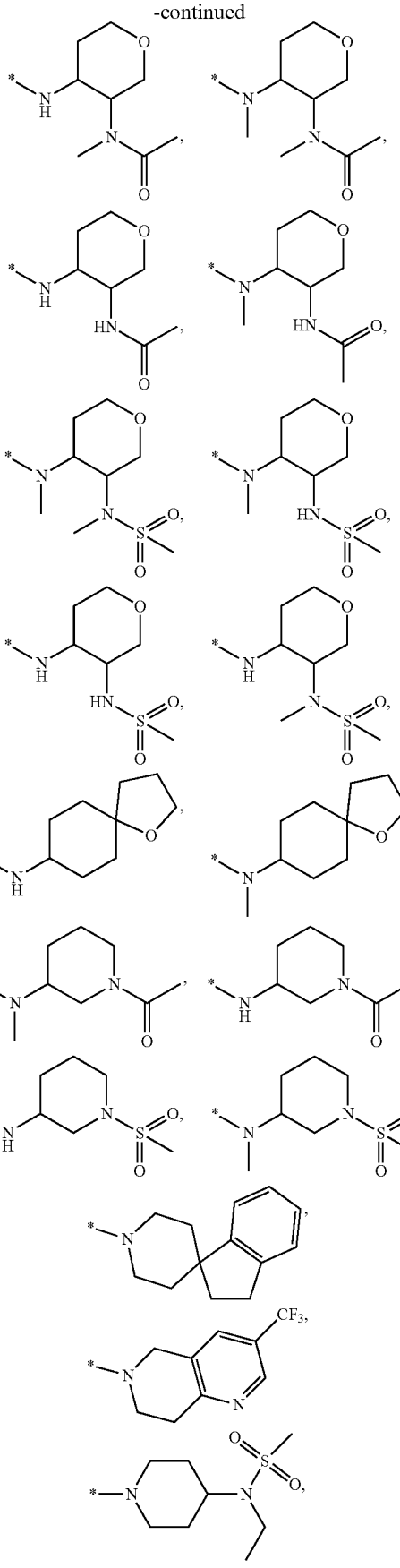

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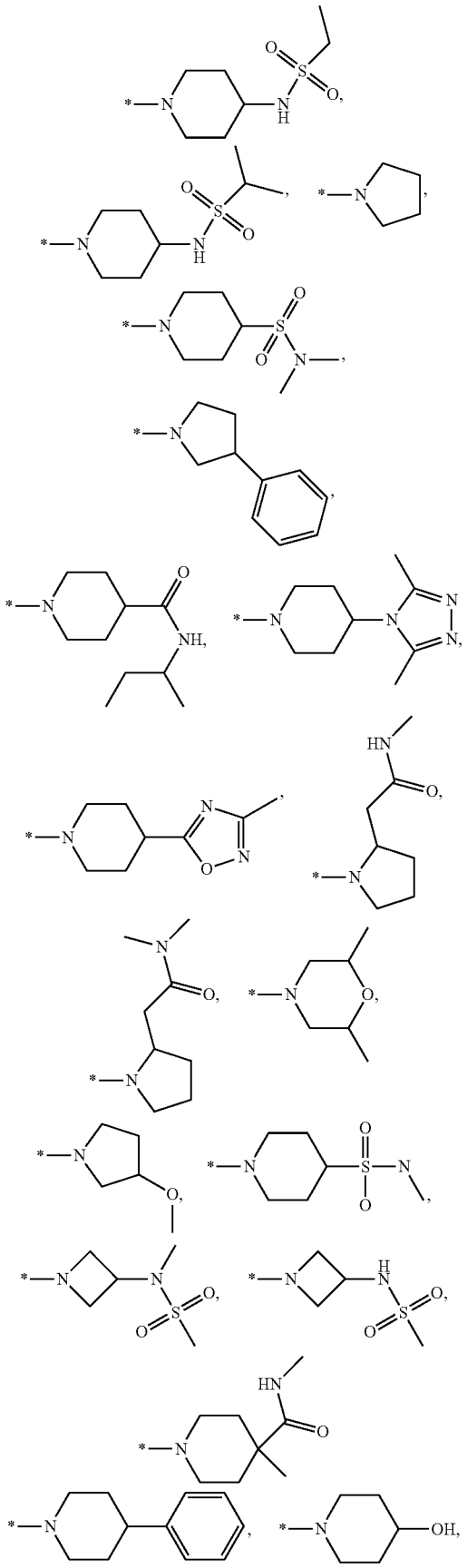

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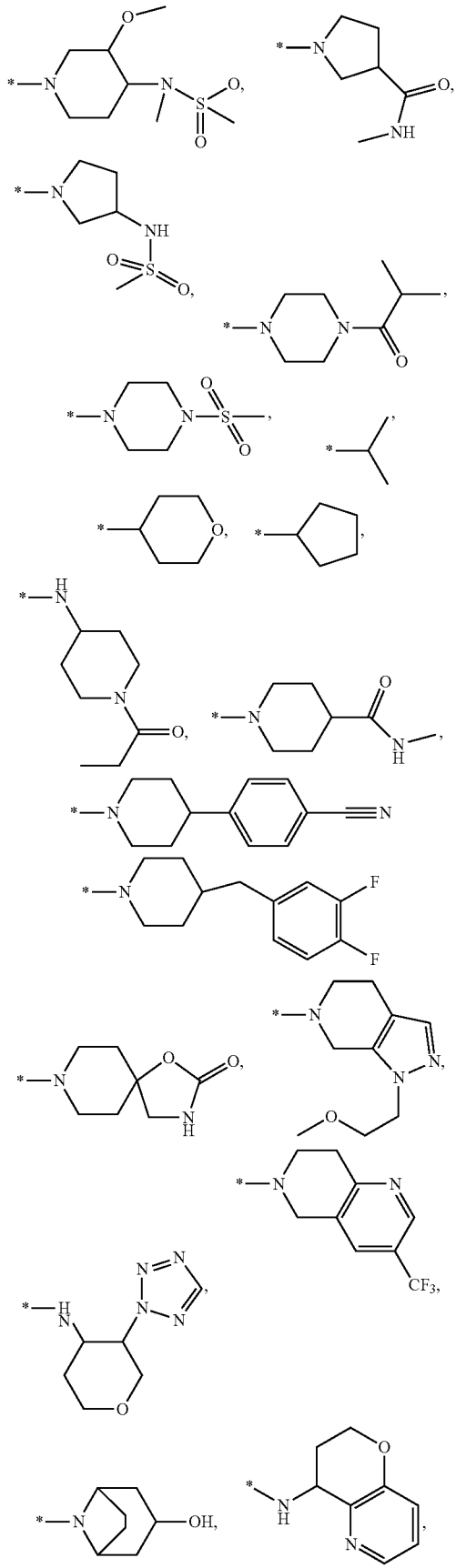

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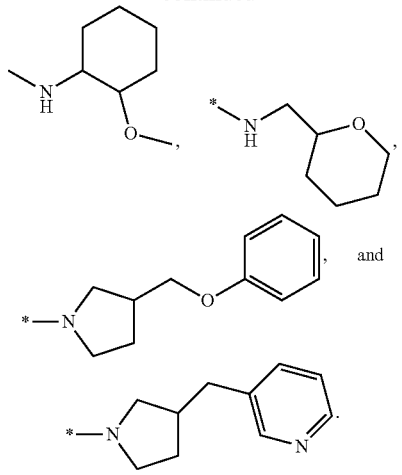


and

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_4, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$, R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, A, L_1, L_2, Z, Q, and n as herein before or below defined, wherein R_5 is selected from among an electron pair, —H, and —C(O)—NH_2.

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_4, R_5, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$, R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, A, L_1, L_2, Z, Q, and n as herein before or below defined, wherein R_6 is selected from among —H, —CH_3, —C_2H_5, —O—CH_3, —O—C_2H_5, —F, —CF_3, and —OCF_3, and more preferred wherein R_6 is selected from among H, and —O—CH_3, and most preferred wherein R_6 is —H.

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$, R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, L_1, L_2, Z, Q, and n as herein before or below defined, wherein A is selected from among a single bond, =CH—, —CH_2, —O—, and —NH—, and more preferred wherein A is selected from among —O— and —NH—, and most preferred wherein A is —NH—.

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$, R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, A, L_1, L_2, Q, and n as herein before or below defined, wherein Z is selected from among C, and N, and more preferred wherein Z is C.

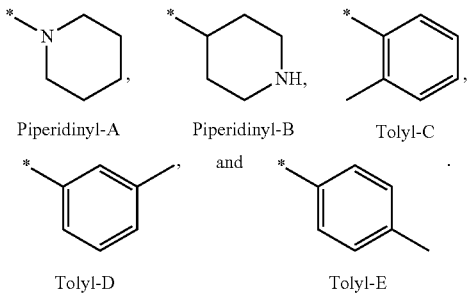
All of the above embodiments under formula (I) have to be understood to optionally be present in form of their individual optical isomers, mixtures of their individual optical isomers, or racemates, as well as in form of their acid addition salts with pharmacologically acceptable acids, as well as in form of their solvates and/or hydrates.

DEFINITIONS

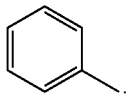
Unless otherwise stated, all the substituents are independent of one another. If for example there might be a plurality of C_1-C_6-alkyl groups as substituents in one group, in the case of three substituents C_1-C_6-alkyl, one may represent methyl, one n-propyl and one tert-butyl.

Within the scope of this application, in the definition of possible substituents, these may also be represented in the form of a structural formula. An asterisk (*) in the structural formula of the substituent is to be understood as being the

linking point to the rest of the molecule. Moreover, the atom of the substituent which follows the linking point is referred to as the atom in position number 1. Thus, for example, the groups N-piperidinyl (Piperidin-A), 4-piperidinyl (Piperidin-B), 2-tolyl (Tolyl-C), 3-tolyl (Tolyl-D), and 4-tolyl (Tolyl-E) are shown as follows:



If there is no asterisk (*) in the structural formula of the substituent, each hydrogen atom may be removed from the substituent and the valency thus freed may act as a binding site to the rest of a molecule. Thus, for example, (Tolyl-F) may represent 2-tolyl, 3-tolyl, 4-tolyl, and benzyl

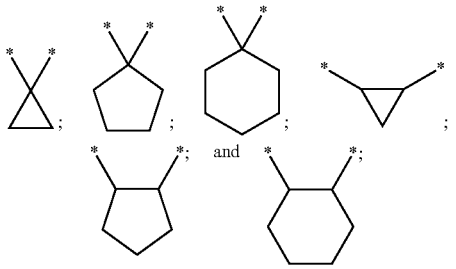


By the term "branched or unbranched, saturated or unsaturated C_1-C_6-carbon chain" it is meant a chain of carbon atoms, which is constituted by six carbon atoms arranged in a row and which can optionally further comprise branches or one or more hetero atoms selected from N, O or S. Said carbon chain can be saturated or unsaturated by comprising double or triple bonds.

By the term "C_1-C_6-alkyl" (including those which are part of other groups) are meant branched and unbranched alkyl groups with 1 to 6 carbon atoms and by the term "C_1-C_4-alkyl" are meant branched and unbranched alkyl groups with 1 to 4 carbon atoms. Alkyl groups with 1 to 4 carbon atoms are preferred. Examples for alkyl groups with 1-6 carbon atoms include: methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl or hexyl. Optionally the abbreviations Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, etc. may also be used for the above-mentioned groups. Unless stated otherwise, the definitions propyl, butyl, pentyl and hexyl include all the possible isomeric forms of the groups in question. Thus, for example, propyl includes n-propyl and iso-propyl, butyl includes iso-butyl, sec-butyl and tert-butyl etc.

By the term "C_1-C_8-alkylene" (including those which are part of other groups) are meant branched and unbranched alkylene groups with 1 to 8 carbon atoms. By the term "C_2-C_8-alkylene" are meant branched and unbranched alkylene groups with 2 to 8 carbon atoms. By the term "C_2-C_6-alkylene" are meant branched and unbranched alkylene groups with 2 to 6 carbon atoms. By the term "C_1-C_4-alkylene" are meant branched and unbranched alkylene groups with 1 to 4 carbon atoms. By the term "C_1-C_2-alkylene" are meant branched and unbranched alkylene groups with 1 to 2 carbon atoms. By the term "C_0-C_4-alkylene" are meant branched and unbranched alkylene groups with 0 to 4 carbon atoms, thus also a single bond is encompassed. By the term "C_1-C_3-alkylene" are meant branched and unbranched alkylene groups with 1 to 3 carbon atoms. Examples for C_1-C_8-alkylene include: methylene, ethylene, propylene, 1-methylethylene, butylene, 1-methylpropylene, 1,1-dimethylethylene, 1,2-dimethylethylene, pentylene, 1,1-dimethylpropylene, 2,2-dimethylpropylene, 1,2-dimethylpropylene, 1,3-dimethylpropylene, hexylene, heptylene or octylene. Unless stated otherwise, the definitions propylene, butylene, pentylene, hexylene, heptylene and octylene include all the possible isomeric forms of the groups in question with the same number of carbons. Thus, for example, propyl also includes 1-methylethylene and butylene includes 1-methylpropylene, 1,1-dimethylethylene, 1,2-dimethylethylene.

If the carbon chain is to be substituted by a group which together with one or two carbon atoms of the alkylene chain forms a carbocyclic ring with 3, 5 or 6 carbon atoms, this includes the following examples of the rings:



By the term "C_2-C_6-alkenyl" (including those which are part of other groups) are meant branched and unbranched alkenyl groups with 2 to 6 carbon atoms and by the term "C_2-C_4-alkenyl" are meant branched and unbranched alkenyl groups with 2 to 4 carbon atoms, provided that they have at least one double bond. Alkenyl groups with 2 to 4 carbon atoms are preferred. Examples for C_2-C_6-alkenyls include: ethenyl or vinyl, propenyl, butenyl, pentenyl, or hexenyl. Unless stated otherwise, the definitions propenyl, butenyl, pentenyl and hexenyl include all the possible isomeric forms of the groups in question. Thus, for example, propenyl includes 1-propenyl and 2-propenyl, butenyl includes 1-, 2- and 3-butenyl, 1-methyl-1-propenyl, 1-methyl-2-propenyl etc.

By the term "methenylene" is meant a group with 1 carbon atom, provided that it is linked by a single bond as well as on the other side by a double bond:

By the term "C_2-C_8-alkenylene" (including those which are part of other groups) are meant branched and unbranched alkenylene groups with 2 to 8 carbon atoms and by the term "C_2-C_6-alkenylene" are meant branched and unbranched alkylene groups with 2 to 6 carbon atoms. By the term "C_1-C_2-alkenylene" are meant alkenylene groups with 1 to 2 carbon atoms, provided that they have at least one double bond, whereas by the term "C_1-alkenylene" is meant "methenylene". Examples for C_2-C_8-alkenylenes include: ethenylene, propenylene, 1-methylethenylene, butenylene, 1-methylpropenylene, 1,1-dimethylethenylene, 1,2-dimethylethenylene, pentenylene, 1,1-dimethylpropenylene,

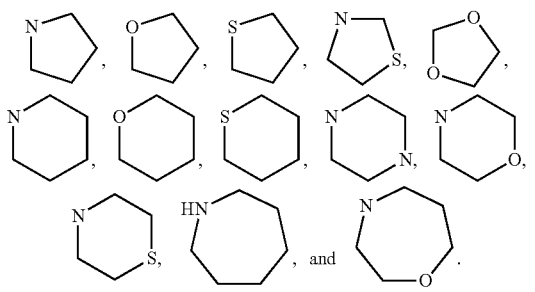
2,2-dimethylpropenylene, 1,2-dimethylpropenylene, 1,3-dimethylpropenylene, hexenylene, heptenylene or octenylene. Unless stated otherwise, the definitions propenylene, butenylene, pentenylene and hexenylene include all the possible isomeric forms of the groups in question with the same number of carbons. Thus, for example, propenyl also includes 1-methylethenylene and butenylene includes 1-methylpropenylene, 1,1-dimethylethenylene, 1,2-dimethylethenylene.

By the term "C_2-C_6-alkynyl" (including those which are part of other groups) are meant branched and unbranched alkynyl groups with 2 to 6 carbon atoms and by the term "C_2-C_4-alkynyl" are meant branched and unbranched alkynyl groups with 2 to 4 carbon atoms, provided that they have at least one triple bond. Examples for C_2-C_6-alkynyls include: ethynyl, propynyl, butynyl, pentynyl or hexynyl. Unless stated otherwise, the definitions propynyl, butynyl, pentynyl and hexynyl include all the possible isomeric forms of the groups in question. Thus for example propynyl includes 1-propynyl and 2-propynyl, butynyl includes 1-, 2-, and 3-butynyl, 1-methyl-1-propynyl, 1-methyl-2-propynyl etc.

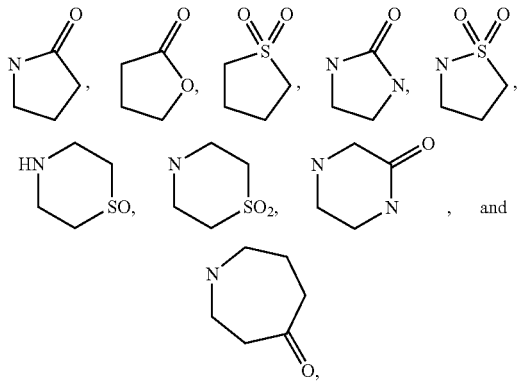
By the term "C_2-C_8-alkynylene" (including those which are part of other groups) are meant branched and unbranched alkynylene groups with 2 to 8 carbon atoms and by the term "C_2-C_6-alkynylene" are meant branched and unbranched alkylene groups with 2 to 6 carbon atoms. Examples of C_2-C_8-alkynylenes include: ethynylene, propynylene, 1-methylethynylene, butynylene, 1-methylpropynylene, 1,1-dimethylethynylene, 1,2-dimethylethynylene, pentynylene, 1,1-dimethylpropynylene, 2,2-dimethylpropynylene, 1,2-dimethylpropynylene, 1,3-dimethylpropynylene, hexynylene, heptynylene or octynylene. Unless stated otherwise, the definitions propynylene, butynylene, pentynylene and hexynylene include all the possible isomeric forms of the groups in question with the same number of carbons. Thus for example propynyl also includes 1-methylethynylene and butynylene includes 1-methylpropynylene, 1,1-dimethylethynylene, 1,2-dimethylethynylene.

By the term "ring" are meant carbocycles, which can be saturated, unsaturated or aromatic and which optionally can comprise one or more hetero atoms selected from N, O or S.

By the term "—C_3-C_8-heterocyclyl" are meant three-, four-, five-, six-, or seven-membered, saturated or unsaturated heterocyclic rings which may contain one, two, or three heteroatoms, selected from among oxygen, sulfur, and nitrogen, while the ring may be linked to the molecule through a carbon atom or through a nitrogen atom, if there is one. By the term "—C_5-C_8-heterocyclyl" are meant five-, six-, or seven-membered, saturated or unsaturated heterocyclic rings which may contain one, two, or three heteroatoms, selected from among oxygen, sulfur, and nitrogen, while the ring may be linked to the molecule through a carbon atom or through a nitrogen atom, if there is one. Examples include:



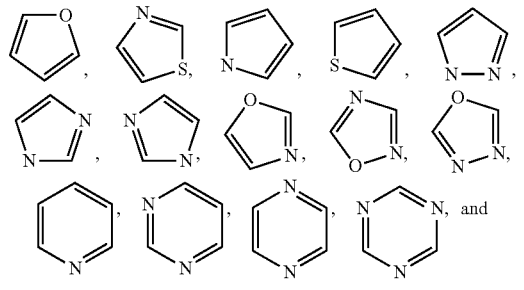
Unless otherwise mentioned, a heterocyclic ring (or "heterocycle") may be provided with a keto group. Examples include:



By the term "C_3-C_8-cycloalkyl" (including those which are part of other groups) are meant cyclic alkyl groups with 3 to 8 carbon atoms. Likewise, by the term "C_3-C_6-cycloalkyl" are meant cyclic alkyl groups with 3 to 6 carbon atoms. Examples of C_3-C_8-cycloalkyls include: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. Unless otherwise stated, the cyclic alkyl groups may be substituted by one or more groups selected from among methyl, ethyl, isopropyl, tert-butyl, hydroxy, fluorine, chlorine, bromine, and iodine.

By the term "aryl" (including those which are part of other groups) are meant aromatic ring systems. By the term "C_5-C_{10}-aryl" (including those which are part of other groups) are meant aromatic ring systems with 5 to 10 carbon atoms. Preferred are "C_6-C_{10}-aryl" groups whereas aromatic rings are meant with 6 to 10 carbon atoms. Examples include: phenyl or naphthyl. Also preferred are "C_5-C_6-aryl" groups whereas aromatic rings are meant with 5 to 6 carbon atoms Unless otherwise stated, the aromatic ring systems may be substituted by one or more groups selected from among methyl, ethyl, iso-propyl, tert-butyl, hydroxy, fluorine, chlorine, bromine and iodine.

By the term "C_5-C_{10}-heteroaryl" (including those which are part of other groups) are meant five- or six-membered heterocyclic aromatic groups or 5-10-membered, bicyclic heteroaryl rings which may contain one, two, or three heteroatoms selected from among oxygen, sulfur, and nitrogen, and contain so many conjugated double bonds that an aromatic system is formed. The following are examples of five- or six- or nine-membered heterocyclic aromatic groups:



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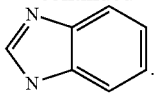
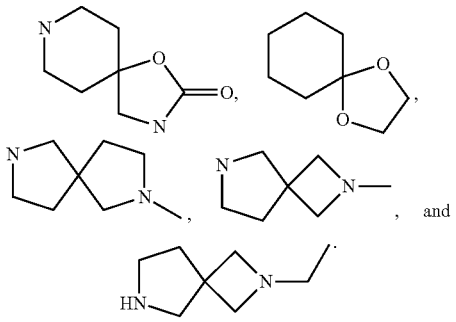


Preferred are "C_5-C_6-heteroaryl" groups whereas aromatic rings are meant five- or six-membered heterocyclic aromatic groups. Unless otherwise stated, these heteroaryls may be substituted by one or more groups selected from among methyl, ethyl, isopropyl, tert-butyl, hydroxy, fluorine, chlorine, bromine, and iodine.

When a generic combined groups are used, for example —X—C_1-C_4-alkyl- with X being a functional group such as —CO—, —NH—, —C(OH)— and the like, the functional group X can be located at either of the ends of the —C_1-C_4-alkyl chain.

By the term "spiro-C_3-C_8-cycloalkyl" (spiro) are meant 3-8 membered, spirocyclic rings while the ring is linked to the molecule through a carbon atom. By the term "spiro-C_3-C_8-heterocyclyl" (spiro) are meant 3-8 membered, spirocyclic rings which may contain one, two, or three heteroatoms selected from among oxygen, sulfur, and nitrogen, while the ring may be linked to the molecule through a carbon atom or through a nitrogen atom, if there is one.

Unless otherwise mentioned, a spirocyclic ring may be provided with an oxo, methyl, or ethyl group. Examples include:



"Halogen" within the scope of the present invention denotes fluorine, chlorine, bromine or iodine. Unless stated to the contrary, fluorine, chlorine and bromine are regarded as preferred halogens.

"Linker" within the scope of the present invention denominates a bivalent group or a bond.

The above listed groups and residues can be combined to form more complex structures composed from carbon chains and rings or the like.

Compounds of general formula (I) may have acid groups, chiefly carboxyl groups, and/or basic groups such as e.g. amino functions. Compounds of general formula (I) may therefore occur as internal salts, as salts with pharmaceutically useable inorganic acids such as hydrochloric acid, sulphuric acid, phosphoric acid, sulphonic acid or organic acids (such as for example maleic acid, fumaric acid, citric acid, tartaric acid or acetic acid) or as salts with pharmaceutically useable bases such as alkali or alkaline earth metal hydroxides or carbonates, zinc or ammonium hydroxides or organic amines such as e.g. diethylamine, triethylamine, triethanolamine inter alia.

As mentioned hereinbefore, the compounds of formula (I) may be converted into the salts thereof, particularly for pharmaceutical use, into the physiologically and pharmacologically acceptable salts thereof. These salts may on the one hand be in the form of the physiologically and pharmacologically acceptable acid addition salts of the compounds of formula (I) with inorganic or organic acids. On the other hand, if R is hydrogen, the compound of formula (I) may also be converted by reaction with inorganic bases into physiologically and pharmacologically acceptable salts with alkali or alkaline earth metal cations as counter ion. The acid addition salts may be prepared for example using hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid. It is also possible to use mixtures of the above-mentioned acids. The alkali and alkaline earth metal salts of the compound of formula (I) are preferably prepared using the alkali and alkaline earth metal hydroxides and hydrides thereof, of which the hydroxides and hydrides of the alkaline earth metals, particularly of sodium and potassium, are preferred and sodium and potassium hydroxide are particularly preferred.

If desired, the compounds of general formula (I) may be converted into the salts thereof, particularly, for pharmaceutical use, into the pharmacologically acceptable acid addition salts with an inorganic or organic acid. Suitable acids include for example succinic acid, hydrobromic acid, acetic acid, fumaric acid, maleic acid, methanesulphonic acid, lactic acid, phosphoric acid, hydrochloric acid, sulphuric acid, tartaric acid or citric acid. It is also possible to use mixtures of the above-mentioned acids.

The invention relates to the compounds in question, optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates, in the form of the tautomers as well as in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids—such as for example acid addition salts with hydrohalic acids—for example hydrochloric or hydrobromic acid or organic acids—such as for example oxalic, fumaric, diglycolic or methanesulphonic acid.

The compounds according to the invention may optionally occur as racemates, but they may also be obtained as pure enantiomers/diastereomers.

The invention relates to the compounds in question, optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates, in the form of the tautomers as well as in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids—such as for example acid addition salts with hydrohalic acids—for example hydrochloric or hydrobromic acid or organic acids—such as for example oxalic, fumaric, diglycolic or methanesulphonic acid.

The compounds according to formula (I) according to the invention have the meanings hereinbefore whereas in particular the preferred embodiments defined by R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$, R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, A, L_1, L_2, Z, Q, and n in each case are independently selected of one another.

Therapeutic Applications

The above exemplary substances have been tested for binding to CCR2 using a binding assay as outlined herein below:

Cell Culture:

THP-1 cells (human acute monocytic leukaemia cells) were cultured under standardized conditions at 37° C. and 5% CO2 in a humidified incubator. THP-1 cells were cultivated in RPMI 1640 medium (Gibco 21875) containing 1% MEM-NEAA (Gibso 11140) 2 mM L-glutamine, 1.5 g/L sodium

bicarbonate, 4.5 g/L glucose, 10 mM HEPES and 1.0 mM sodium pyruvate, 90%; 10% fetal calf serum (FCS Gibco 10500-064).

Membranes were prepared from THP-1 cells. THP-1 cells were centrifuged at 300×g at 4° C. for 10 min. The cell pellet was resuspended in Phosphate Buffer Saline (PBS, including 10 μM Pefabloc and a protease inhibitor mix 'complete', Boehringer Mannheim (1 tablet/50 ml)), to a concentration of 80 cells/ml. The membrane preparation was performed by disrupting the cells by nitrogen decomposition (at 50 bar, for 1 h) in a "Nitrogen Bombe" (Parr Instrument). Cell debris was removed by centrifugation (800×g at 4° C., 1 min) The supernatant was centrifuged at 80000×g, 4° C. for 30 min to sediment the cell membranes. Usually 50 mg of protein (Bradford assay) were yielded from 1×10E9 cells. The membranes were resuspended in 25 mM HEPES, 25 mM MgCl2, 1 mM CaCl2, 10% Glycerine for storage in aliquots at −80° C. in 25 mM HEPES, 25 mM MgCl2, 1 mM CaCl2, 10% Glycerine and stored at −80° C.

Receptor Membrane Binding Assay:

Perkin Elmer NEX 332 Jod 125 MCP-1, Stock: 2200 Ci/mmol solved in 2000 μl assay buffer, stored at −20° C. THP-1 membrane were adjusted with 25 mM HEPES, pH 7.2; 5 mM MgCl2; 0.5 mM CaCl2; 0.2% BSA assay buffer to a concentration of 2.5 μg/15 μl. Amersham Biosciences PVT-WGA Beads (RPNQ0001) were adjusted with assay buffer to a concentration of 0.24 mg/30 μl. For preparation of the membrane-bead-suspension membranes and beads were incubated for 30 min at RT under rotation (60 rpm) with a ratio of 1:2. Test compounds dissolved in 100% DMSO to a concentration of 10 mM and are further diluted with 100% DMSO to 1 mM. All additional compound dilutions were obtained with assay buffer, final 1% DMSO. Compounds, membrane-bead-suspension and [125I]MCP-1 (ca. 25000 cpm/10 μl) were incubated. Bound radioactivity was determined by scintillation counter after 8 h. Determination of affinity of test compounds (dissociation constant hKi) is calculated by iterative fitting of experimental data using the "easy sys" program, which is based on law of mass action (Schittkowski K. (1994), Numerische Mathematik, Vol. 68, 129-142).

All of the above-referenced examples have been found to have an activity in this assay of 10 μM or less.

Example	hKi	CCR2 % ctrl @ 10 μM	Example	hKi	CCR2 % ctrl @ 10 μM
1	32	1	15	200	14
2	222	13	16	1904	40
3	204	14	17	302	18
4	1593	43	18	3505	52
5	616	26	19	269	40
6	1928	41	20	303	24
7	306	16	21	2660	51
8	1023	36	22	466	24
9	974	32	23	169	7
10	650	27	24	4029	58
11	1710	38	25	2406	47
12	664	29	26	914	30
13	1332	42	27	620	25
14	387	22	28	4176	58
29	2097	40	59	55	5
30	446	18	60	44	5
31	790	28	61	46	2
32	37	2	62	38	3
33	22	0	63	54	7
34	62	4	64	65	8
35	24	5	65	176	8
36	10	1	66	138	8
37	11	4	67	1423	27
38	69	13	68	98	7
39	36	2	69	63	7
40	174	9	70	80	6
41	11	6	71	117	12
42	433	16	72	81	7
43	566	17	73	38	2
44	1639	27	74	71	2
45	501	17	75	67	7
46	225	12	76	132	12
47	222	14	77	650	27
48	1778	26	78	740	28
49	97	7	79	89	10
50	928	22	80	53	7
51	290	13	81	52	8
52	175	12	82	43	4
53	18	4	83	43	3
54	356	13	84	69	4
55	200	17	85	55	13
56	127	8	86	39	3
57	93	10	87	78	9
58	336	12	88	58	6
89	770	29	119	1033	37
90	127	10	120	499	30
91	236	23	121	147	15
92	175	14	122	415	23
93	123	6	123	542	26
94	211	8	124	361	20
95	170	2	125	446	25
96	939	21	126	399	23
97	665	17	127	665	35
98	214	2	128	445	26
99	1826	32	129	336	21
100	395	18	130	4266	50
101	986	35	131	55	6
102	224	15	132	672	31
103	1605	30	133	205	15
104	617	31	134	399	23
105	687	31	135	888	19
106	405	13	136	773	14
107	232	12	137	634	14
108	627	20	138	145	6
109	213	11	139	443	9
110	527	28	140	692	16
111	464	27	141	422	7
112	378	21	142	529	8
113	3306	46	143	422	8
114	62	8	144	91	7
115	847	33	145	181	17
116	198	16	146	3	7
117	285	19	147	40	8
118	2162	41	148	119	4
149	41	10	179	1637	42
150	12	3	189	4812	60
151	14	7	181	3607	58
152	44	7	182	2991	53
153	27	1	183	426	45
154	123	15	184	908	30
155	76	8	185	4209	53
156	18	8	186	78	8
157	1147	23	187	256	15
158	6	0	188	3934	53
159	25	4	189	170	13
160	43	3	190	783	27
161	1996	30	191	519	20
162	3798	43	192	1446	37
163	1560	32	193	1536	35
164	353	15	194	491	25
165	222	15	195	141	14
166	227	16	196	666	19
167	246	16	197	33	4
168	51	9	198	58	1
169	2287	54	199	534	9
170	705	31	200	108	5
171	356	16	201	101	6
172	736	28	202	292	7
173	89	6	203	641	11
174	2718	53	204	123	6
175	434	14	205	135	11
176	648	31	206	44	3

-continued

177	1252	43	207	1180	35
178	27	0	208	99	7
209	177	7	239	2319	33
210	83	0	240	104	7
211	140	5	241	522	21
212	731	24	242	516	21
213	430	14	243	1615	40
214	711	20	244	366	24
215	2146	42	245	555	15
216	4283	59	246	306	2
217	4326	54	247	149	6
218	281	8	248	576	17
219	476	22	249	3249	36
220	979	27	250	1263	32
221	172	12	251	439	75
222	1306	31	252	38	6
223	244	14	253	350	17
224	1230	35	254	101	11
225	21	0	255	33	5
226	1170	36	256	438	25
227	333	22	257	186	14
228	331	16	258	64	4
229	1133	39	259	277	16
230	1845	45	260	493	20
231	215	15	261	120	8
232	924	34	262	224	13
233	194	8	263	1968	27
234	401	19	264	41	3
235	460	26	265	462	23
236	175	14	266	149	
237	133	9	267	487	20
238	239	14	268	119	5
228a	1564	9	228e	3720	40
228b	2	4	228f	15	1
228c	29	0	228g	169	6
228d	91	1	228h	5	0
269	2340	36	285	1306	35
270	179	9	286	965	19
271	1608	15	287	2547	33
272	155	8	288	738	13
273	1435	27	289	1667	34
274	4421	48	290	1601	28
275	593	19	291	3123	32
276	1842	23	292	136	15
277	1376	34	293	717	27
278	1078	32	294	230	16
279	192	9	295	140	0
280	1435	32	296	69	3
281	1012	24	297	164	10
282	1527	39	298	599	17
283	4421	48	299	70	6
284	1514	42	300	136	8
275a	29	0	275c	2932	38
275b	26	3	275d	318	10

Example	hKi	Example	hKi
228go	54	159e	28
228gp	1354	159f	14
228ga	23	159g	15
228gb	3828	159h	39
228gc	561	159i	24
228gd	1094	159k	22
228ge	37	159l	22
228gf	145	159m	9
228gg	1026	159n	233
228gh	4066	159o	12
228gi	1101	159p	7
228gj	55	159q	10
228gk	44	159r	2578
228gl	537	159s	1314
228gm	28	159t	1202
228gn	333	159u	29
275da	4	159w	9
275db	33	159y	169
275dc	11	159x	147
275dd	40	159z	11
275de	16	159aa	18
275df	15	159ba	11

-continued

275dg	12	159ca	3
275dh	3	159da	5
275di	1	159ea	7
275dj	4	159fa	35
159a	10	159ga	28
159b	7	159ha	27
159c	13	159ia	17
159d	15	159ja	18
159ka	19	159pb	10
159la	19	159qb	69
159ma	20	159rb	54
159na	21	159sb	21
159oa	29	159tb	13
159pa	32	159ub	18
159qa	19	159wb	16
159ra	22	159yb	15
159sa	22	159xb	6
159ta	27	159zb	15
159ua	23	159ac	5936
159wa	33	159bc	3492
159ya	18	159cc	10
159xa	21	159dc	38
159za	6	159ec	961
159ab	27	159fc	13
159bb	48	159gc	26
159cb	39	228ha	32
159db	16	301	22
159eb	72	302	32
159fb	199	275dk	17
159gb	39	275dl	372
159hb	20		
159ib	15		
159jb	39		
159kb	24		
159lb	12		
159mb	14		
159nb	88		
159ob	118		

Based on the ability of the substances described by formula (I) to effectively bind to CCR2 a range of therapeutic applications can be envisaged. The present invention provides a method for modulating or treating at least one MCP-1 related disease, in a cell, tissue, organ, animal, or patient, as known in the art or as described herein, using at least one CCR2 antagonist of the present invention. The present invention also provides a method for modulating or treating at least one MCP-1 related disease, in a cell, tissue, organ, animal, or patient including, but not limited to, at least one of malignant disease, metabolic disease, an immune or inflammatory related disease, a cardiovascular disease, an infectious disease, or a neurologic disease. Such conditions are selected from, but not limited to, diseases or conditions mediated by cell adhesion and/or angiogenesis. Such diseases or conditions include an immune disorder or disease, a cardiovascular disorder or disease, an infectious, malignant, and/or neurologic disorder or disease, or other known or specified MCP-1 related conditions. In particular, the CCR2 antagonists are useful for the treatment of diseases that involve inflammation such as COPD, angiogenesis such as disease of the eye and neoplastic disease, tissue remodeling such as restenosis, and proliferation of certain cells types particularly epithelial and squamous cell carcinomas. Particular indications include use in the treatment of atherosclerosis, restenosis, cancer metastasis, rheumatoid arthritis, diabetic retinopathy and macular degeneration. The antagonists may also be useful in the treatment of various fibrotic diseases such as idiopathic pulmonary fibrosis, diabetic nephropathy, hepatitis, and cirrhosis. Thus, the present invention provides a method for modulating or treating at least one CCR2 related disease, in a cell, tissue, organ, animal, or patient, as known in the art or as described

herein, using at least one CCR2 antagonist of the present invention. Particular indications are discussed below:

Pulmonary Diseases

The present invention also provides a method for modulating or treating at least one malignant disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: pneumonia; lung abscess; occupational lung diseases caused be agents in the form or dusts, gases, or mists; asthma, bronchiolitis fibrosa obliterans, respiratory failure, hypersensitivity diseases of the lungs including hypersensitivity pneumonitis (extrinsic allergic alveolitis), allergic bronchopulmonary aspergillosis, and drug reactions; adult respiratory distress syndrome (ARDS), Goodpasture's Syndrome, chronic obstructive airway disorders (COPD), idiopathic interstitial lung diseases such as idiopathic pulmonary fibrosis and sarcoidosis, desquamative interstitial pneumonia, acute interstitial pneumonia, respiratory bronchiolitis-associated interstitial lung disease, idiopathic bronchiolitis obliterans with organizing pneumonia, lymphocytic interstitial pneumonitis, Langerhans' cell granulomatosis, idiopathic pulmonary hemosiderosis; acute bronchitis, pulmonary alveolar, proteinosis, bronchiectasis, pleural disorders, atelectasis, cystic fibrosis, and tumors of the lung, and pulmonary embolism.

Malignant Diseases

The present invention also provides a method for modulating or treating at least one malignant disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: leukemia, acute leukemia, acute lymphoblastic leukemia (ALL), B-cell, T-cell or FAB ALL, acute myeloid leukemia (AML), chromic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodyplastic syndrome (MDS), a lymphoma, Hodgkin's disease, a malignant lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, Kaposi's sarcoma, colorectal carcinoma, pancreatic carcinoma, renal cell carcinoma, breast cancer, nasopharyngeal carcinoma, malignant histiocytosis, paraneoplastic syndrome/hypercalcemia of malignancy, solid tumors, adenocarcinomas, squamous cell carcinomas, sarcomas, malignant melanoma, particularly metastatic melanoma, hemangioma, metastatic disease, cancer related bone resorption, cancer related bone pain, and the like.

Immune Related Diseases

The present invention also provides a method for modulating or treating at least one immune related disease, in a cell, tissue, organ, animal, or patient including, but not limited to, at least one of rheumatoid arthritis, juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondilitis, gastric ulcer, seronegative arthropathies, osteoarthritis, inflammatory bowel disease, ulcerative colitis, systemic lupus erythematosis, antiphospholipid syndrome, iridocyclitisluveitisloptic neuritis, idiopathic pulmonary fibrosis, systemic vasculitis/wegener's granulomatosis, sarcoidosis, orchitislvasectomy reversal procedures, allergiclatopic diseases, asthma, allergic rhinitis, eczema, allergic contact dermatitis, allergic conjunctivitis, hypersensitivity pneumonitis, transplants, organ transplant rejection, graft-versus-host disease, systemic inflammatory response syndrome, sepsis syndrome, gram positive sepsis, gram negative sepsis, culture negative sepsis, fungal sepsis, neutropenic fever, urosepsis, meningococcemia, traumalhemo~~hage, burns, ionizing radiation exposure, acute pancreatitis, adult respiratory distress syndrome, rheumatoid arthritis, alcohol-induced hepatitis, chronic inflammatory pathologies, sarcoidosis, Crohn's pathology, sickle cell anemia, diabetes, nephrosis, atopic diseases, hypersensitivity reactions, allergic rhinitis, hay fever, perennial rhinitis, conjunctivitis, endometriosis, asthma, urticaria, systemic anaphalaxis, dermatitis, pernicious anemia, hemolytic diseases, thrombocytopenia, graft rejection of any organ or tissue, kidney transplant rejection, heart transplant rejection, liver transplant rejection, pancreas transplant rejection, lung transplant rejection, bone marrow transplant (BMT) rejection, skin allograft rejection, cartilage transplant rejection, bone graft rejection, small bowel transplant rejection, fetal thymus implant rejection, parathyroid transplant rejection, xenograft rejection of any organ or tissue, allograft rejection, anti-receptor hypersensitivity reactions, Graves disease, Raynoud's disease, type B insulin-resistant diabetes, asthma, myasthenia gravis, antibody-meditated cytotoxicity, type IU hypersensitivity reactions, systemic lupus erythematosus, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes syndrome, antiphospholipid syndrome, pemphigus, scleroderma, mixed connective tissue disease, idiopathic Addison's disease, diabetes mellitus, chronic active hepatitis, primary billiary cirrhosis, vitiligo, vasculitis, post-MI cardiotomy syndrome, type IV hypersensitivity, contact dermatitis, hypersensitivity pneumonitis, allograft rejection, granulomas due to intracellular organisms, drug sensitivity, metabolic/idiopathic, Wilson's disease, hemachromatosis, alpha-1-antitrypsin deficiency, diabetic retinopathy, hashimoto's thyroiditis, osteoporosis, hypothalamic-pituitary-adrenal axis evaluation, primary billiary cirrhosis, thyroiditis, encephalomyelitis, cachexia, cystic fibrosis, neonatal chronic lung disease, chronic obstructive pulmonary disease (COPD), familial hematophagocytic lymphohistiocytosis, dermatologic conditions, psoriasis, alopecia, nephrotic syndrome, nephritis, glomerular nephritis, acute renal failure, hemodialysis, uremia, toxicity, preeclampsia, OKT3 therapy, anti-CD3 therapy, cytokine therapy, chemotherapy, radiation therapy (e.g., including but not limited toasthenia, anemia, cachexia, and the like), chronic salicylate intoxication, and the like.

Cardiovascular Diseases

The present invention also provides a method for modulating or treating at least one cardiovascular disease in a cell, tissue, organ, animal, or patient, including, but not limited to, at least one of cardiac 25 stun syndrome, myocardial infarction, congestive heart failure, stroke, ischemic stroke, hemorrhage, arteriosclerosis, atherosclerosis, restenosis, diabetic arteriosclerotic disease, hypertension, arterial hypertension, renovascular hypertension, syncope, shock, syphilis of the cardiovascular system, heart failure, cor pulmonale, primary pulmonary hypertension, cardiac arrhythmias, atrial ectopic beats, atrial flutter, atrial fibrillation (sustained or paroxysmal), post perfusion syndrome, cardiopulmonary bypass inflammation response, chaotic or multifocal atrial tachycardia, regular narrow QRS tachycardia, specific arrythmias, ventricular fibrillation, His bundle arrythmias, atrioventricular block, bundle branch block, myocardial ischemic disorders, coronary artery disease, angina pectoris, myocardial infarction, cardiomyopathy, dilated congestive cardiomyopathy, restrictive cardiomyopathy, valvular heart diseases, endocarditis, pericardial disease, cardiac tumors, aordic and peripheral aneuryisms, aortic dissection, inflammation of the aorta, occlusion of the abdominal aorta and its branches, peripheral vascular disorders, occlusive arterial disorders, peripheral atherosclerotic disease, thromboangiitis obliterans, functional peripheral arterial disorders, Raynaud's phenomenon and disease, acrocyanosis, erythromelalgia, venous diseases, venous thrombosis, varicose veins, arteriovenous

fistula, lymphederma, lipedema, unstable angina, reperfusion injury, post pump syndrome, ischemia-reperfusion injury, and the like. Such a method can optionally comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one CCR2 antagonist to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.

Neurologic Diseases

The present invention also provides a method for modulating or treating at least one neurologic disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: Neuropathic pain such as low back pain, hip pain, leg pain, non-herpetic neuralgia, post herpetic neuralgia, diabetic neuropathy, nerve injury-induced pain, acquired immune deficiency syndrome (AIDS) related neuropathic pain, head trauma, toxin and chemotherapy caused nerve injuries, phantom limb pain, multiple sclerosis, root avulsions, painful traumatic mononeuropathy, painful polyneuropathy, thalamic pain syndrome, post-stroke pain, central nervous system injury, post surgical pain, carpal tunnel syndrome, trigeminal neuralgia, post mastectomy syndrome, postthoracotomy syndrome, stump pain, repetitive motion pain, neuropathic pain associated hyperalgesia and allodynia, alcoholism and other drug-induced pain; neurodegenerative diseases, multiple sclerosis, migraine headache, AIDS dementia complex, demyelinating diseases, such as multiple sclerosis and acute transverse myelitis; extrapyramidal and cerebellar disorders' such as lesions of the corticospinal system; disorders of the basal ganglia or cerebellar disorders; hyperkinetic movement disorders such as Huntington's Chorea and senile chorea; drug-induced movement disorders, such as those induced by drugs which block CNS dopamine receptors; hypokinetic movement disorders, such as Parkinson's disease; Progressive supra-nucleo Palsy; structural lesions of the cerebellum; spinocerebellar degenerations, such as spinal ataxia, Friedreich's ataxia, cerebellar cortical degenerations, multiple systems degenerations (Mencel, Dejerine-Thomas, Shi-Drager, and Machado-Joseph); systemic disorders (Refsum's disease, abetalipoprotemia, ataxia, telangiectasia, and mitochondrial multi.system disorder); demyelinating core disorders, such as multiple sclerosis, acute transverse myelitis; and disorders of the motor unit' such as neurogenic muscular atrophies (anterior horn cell degeneration, such as amyotrophic lateral sclerosis, infantile spinal muscular atrophy and juvenile spinal muscular atrophy); Alzheimer's disease; Down's Syndrome in middle age; Diffuse Lewy body disease; Senile Dementia of Lewy body type; Wernicke-Korsakoff syndrome; chronic alcoholism; Creutzfeldt-Jakob disease; Subacute sclerosing panencephalitis, Hallerrorden-Spatz disease; and Dementia pugilistica, and the like.

Fibrotic Conditions

In addition to the above described conditions and diseases, the present invention also provides a method for modulating or treating fibrotic conditions of various etiologies such as liver fibrosis (including but not limited to alcohol-induced cirrhosis, viral-induced cirrhosis, autoimmune-induced hepatitis); lung fibrosis (including but not limited to scleroderma, idiopathic pulmonary fibrosis); kidney fibrosis (including but not limited to scleroderma, diabetic nephritis, glomerular pehpritis, lupus nephritis); dermal fibrosis (including but not limited to scleroderma, hypertrophic and keloid scarring, burns); myelofibrosis; Neurofibromatosis; fibroma; intestinal fibrosis; and fibrotic adhesions resulting from surgical procedures.

The present invention also provides a method for modulating or treating at least one wound, trauma or tissue injury or chronic condition resulting from or related thereto, in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: bodily injury or a trauma associated with surgery including thoracic, abdominal, cranial, or oral surgery; or wherein the wound is selected from the group consisting of aseptic wounds, contused wounds, incised wounds, lacerated wounds, non-penetrating wounds, open wounds, penetrating wounds, perforating wounds, puncture wounds, septic wounds, infarctions and subcutaneous wounds; or wherein the wound is selected from the group consisting of ischemic ulcers, pressure sores, fistulae, severe bites, thermal burns and donor site wounds; or wherein the wound is an aphthous wound, a traumatic wound or a herpes associated wound. Donor site wounds are wounds which e.g. occur in connection with removal of hard tissue from one part of the body to another part of the body e.g. in connection with transplantation. The wounds resulting from such operations are very painful and an improved healing is therefore most valuable. Wound fibrosis is also amenable to CCR2 antagonist therapy as the first cells to invade the wound area are neutrophils followed by monocytes which are activated by macrophages. Macrophages are believed to be essential for efficient wound healing in that they also are responsible for phagocytosis of pathogenic organisms and a clearing up of tissue debris. Furthermore, they release numerous factors involved in subsequent events of the healing process. The macrophages attract fibroblasts which start the production of collagen. Almost all tissue repair processes include the early connective tissue formation, a stimulation of this and the subsequent processes improve tissue healing, however, overproduction of connective tissue and collagen can lead to a fibrotic tissue characterized as inelastic and hypoxic. The CCR2 antagonist of the invention can be used in methods for modulating, treating or preventing such sequalae of wound healing.

Other Therapeutic Uses of CCR2 Antagonists

The present invention also provides a method for modulating or treating at least one infectious disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of:

acute or chronic bacterial infection, acute and chronic parasitic or infectious processes, including bacterial, viral and fungal infections, HIV infection, HIV neuropathy, meningitis, hepatitis (A, B or C, or the like), septic arthritis, peritonitis, pneumonia, epiglottitis, *e. coli* 0157:h7, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, malaria, dengue hemorrhagic fever, leishmaniasis, leprosy, toxic shock syndrome, streptococcal myositis, gas gangrene, *mycobacterium tuberculosis, mycobacterium avium intracellulare, pneumocystis carinii* pneumonia, pelvic inflammatory disease, orchitislepidydimitis, legionella, lyme disease, influenza a, epstein-barr virus, vital-associated hemaphagocytic syndrome, vital encephalitisiaseptic meningitis, and the like.

Any method of the present invention can comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one CCR2 antagonist to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like.

Combinations The compounds of formula I may be used on their own or in conjunction with other active substances of formula I according to the invention. If desired the compounds of formula I may also be used in combination with other pharmacologically active substances. It is preferable to use for this purpose active substances selected for example

from among betamimetics, anticholinergics, corticosteroids, other PDE4-inhibitors, LTD4-antagonists, EGFR-inhibitors, MRP4-inhibitors, dopamine agonists, H1-antihistamines, PAF-antagonists and PI3-kinase inhibitors or double or triple combinations thereof, such as for example combinations of compounds of formula I with one or two compounds selected from among

- betamimetics, corticosteroids, PDE4-inhibitors, EGFR-inhibitors and LTD4-antagonists,
- anticholinergics, betamimetics, corticosteroids, PDE4-inhibitors, EGFR-inhibitors and LTD4-antagonists,
- PDE4-inhibitors, corticosteroids, EGFR-inhibitors and LTD4-antagonists
- EGFR-inhibitors, PDE4-inhibitors and LTD4-antagonists
- EGFR-inhibitors and LTD4-antagonists
- CCR3-inhibitors, iNOS-inhibitors (inducible nitric oxide synthase-inhibitors), (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (hereinafter referred to as "BH4") and the derivatives thereof as mentioned in WO 2006/120176 and SYK-inhibitors (spleen tyrosine kinase-inhibitors)
- anticholinergics, betamimetics, corticosteroids, PDE4-inhibitors and MRP4-inhibitors.

The invention also encompasses combinations of three active substances, each selected from one of the above-mentioned categories of compounds.

The betamimetics used are preferably compounds selected from among albuterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, fenoterol, formoterol, arformoterol, zinterol, hexoprenaline, ibuterol, isoetharine, isoprenaline, levosalbutamol, mabuterol, meluadrine, metaproterenol, orciprenaline, pirbuterol, procaterol, reproterol, rimiterol, ritodrine, salmeterol, salmefamol, soterenol, sulphonterol, tiaramide, terbutaline, tolubuterol, CHF-1035, HOKU-81, KUL-1248, 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzyl-sulphonamide, 5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one, 4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl]sulphonyl}ethyl]-amino}ethyl]-2(3H)-benzothiazolone, 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol, 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-tert.-butylamino)ethanol, 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetate ethyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1,1dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethyl amino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid, 8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one and 1-(4-ethoxy-carbonylamino-3-cyano-5-fluorophenyl)-2-(tert.-butylamino)ethanol, optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof.

Preferably the beta mimetics are selected from among bambuterol, bitolterol, carbuterol, clenbuterol, fenoterol, formoterol, hexoprenaline, ibuterol, pirbuterol, procaterol, reproterol, salmeterol, sulphonterol, terbutaline, tolubuterol, 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulphonamide, 5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one, 4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl]sulphonyl}ethyl]-amino}ethyl]-2(3H)-benzothiazolone, 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol, 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-tert.-butylamino)ethanol, 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetate ethyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1,1dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethyl amino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid, 8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one and 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-(tert.-butylamino)ethanol, optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof.

Particularly preferred betamimetics are selected from among fenoterol, formoterol, salmeterol, 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulphonamide, 5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-

quinolin-2-one, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetate ethyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1,1dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid, 8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one and 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol, optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof.

Of these betamimetics those which are particularly preferred according to the invention are formoterol, salmeterol, 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulphonamide, 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(ethyl 4-phenoxy-acetate)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1,1dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid, 8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one and 5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one, optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof.

According to the invention the acid addition salts of the betamimetics are preferably selected from among hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonat, preferably hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate. Of the above-mentioned acid addition salts the salts of hydrochloric acid, methanesulphonic acid, benzoic acid and acetic acid are particularly preferred according to the invention.

The anticholinergics used are preferably compounds selected from among the tiotropium salts, oxitropium salts, flutropium salts, ipratropium salts, glycopyrronium salts, trospium salts, tropenol 2,2-diphenylpropionate methobromide, scopine 2,2-diphenylpropionate methobromide, scopine 2-fluoro-2,2-diphenylacetate methobromide, tropenol 2-fluoro-2,2-diphenylacetate methobromide, tropenol 3,3',4,4'-tetrafluorobenzilate methobromide, scopine 3,3',4,4'-tetrafluorobenzilate methobromide, tropenol 4,4'-difluorobenzilate methobromide, scopine 4,4'-difluorobenzilate methobromide, tropenol 3,3'-difluorobenzilate methobromide, -scopine 3,3'-difluorobenzilate methobromide, tropenol 9-hydroxy-fluorene-9-carboxylate-methobromide, tropenol 9-fluoro-fluorene-9-carboxylate-methobromide, scopine 9-hydroxy-fluoren-9-carboxylate methobromide, scopine 9-fluoro-fluorene-9-carboxylate methobromide, tropenol 9-methyl-fluorene-9-carboxylate methobromide, scopine 9-methyl-fluorene-9-carboxylate methobromide, cyclopropyltropine benzilate methobromide, cyclopropyltropine 2,2-diphenylpropionate methobromide, cyclopropyltropine 9-hydroxy-xanthene-9-carboxylate methobromide, cyclopropyltropine 9-methyl-fluorene-9-carboxylate methobromide, cyclopropyltropine 9-methyl-xanthene-9-carboxylate methobromide, cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate methobromide, methyl-cyclopropyltropine 4,4'-difluorobenzilate methobromide, tropenol 9-hydroxy-xanthene-9-carboxylate-methobromide, scopine 9-hydroxy-xanthene-9-carboxylate methobromide, tropenol 9-methyl-xanthene-9-carboxylate methobromide, scopine 9-methyl-xanthene-9-carboxylate methobromide, tropenol 9-ethyl-xanthene-9-carboxylate methobromide, tropenol 9-difluoromethyl-xanthene-9-carboxylate methobromide, scopine 9-hydroxymethyl-xanthene-9-carboxylate methobromide, optionally in the form of the solvates or hydrates thereof.

In the above-mentioned salts the cations tiotropium, oxitropium, flutropium, ipratropium, glycopyrronium and trospium are the pharmacologically active ingredients. As anions, the above-mentioned salts may preferably contain chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate or p-toluenesulphonate, while chloride, bromide, iodide, sulphate, methanesulphonate or p-toluenesulphonate are preferred as counter-ions. Of all the salts, the chlorides, bromides, iodides and methanesulphonate are particularly preferred.

Of particular importance is tiotropium bromide. In the case of tiotropium bromide the pharmaceutical combinations according to the invention preferably contain it in the form of the crystalline tiotropium bromide monohydrate, which is known from WO 02/30928. If the tiotropium bromide is used in anhydrous form in the pharmaceutical combinations according to the invention, it is preferable to use anhydrous crystalline tiotropium bromide, which is known from WO 03/000265.

Corticosteroids used here are preferably compounds selected from among prednisolone, prednisone, butixocort-

propionate, flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, rofleponide, dexamethasone, betamethasone, deflazacort, RPR-106541, NS-126, (S)-fluoromethyl 6,9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxo-androsta-1,4-diene-17-carbothionate and

(S)-(2-oxo-tetrahydro-furan-3S-yl) 6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-propionyloxy-androsta-1,4-diene-17-carbothionate, optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.

Particularly preferred is the steroid selected from among flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, rofleponide, dexamethasone, NS-126, (S)-fluoromethyl 6,9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxo-androsta-1,4-diene-17-carbothionate and (S)-(2-oxo-tetrahydro-furan-3S-yl) 6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-propionyloxy-androsta-1,4-diene-17-carbothionate, optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.

Particularly preferred is the steroid selected from among budesonide, fluticasone, mometasone, ciclesonide and (S)-fluoromethyl 6,9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxo-androsta-1,4-diene-17-carbothionate, optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.

Any reference to steroids includes a reference to any salts or derivatives, hydrates or solvates thereof which may exist. Examples of possible salts and derivatives of the steroids may be: alkali metal salts, such as for example sodium or potassium salts, sulphobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates thereof.

Other PDE4 inhibitors which may be used are preferably compounds selected from among enprofyllin, theophyllin, roflumilast, ariflo (cilomilast), tofimilast, pumafentrin, lirimilast, arofyllin, atizoram, D-4396 (Sch-351591), AWD-12-281 (GW-842470), NCS-613, CDP-840, D-4418, PD-168787, T-440, T-2585, V-11294A, C1-1018, CDC-801, CDC-3052, D-22888, YM-58997, Z-15370, N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropyl-methoxybenzamide, (−)p-[(4aR*,10bS*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[s][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide, (R)-(+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone, 3-(cyclopentyloxy-4-methoxyphenyl)-1-(4-N'-[N-2-cyano-S-methyl-isothioureido]benzyl)-2-pyrrolidone, cis[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid], 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-one, cis[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol], (R)-(+)-ethyl[4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-ylidene]acetate, (S)-(−)-ethyl [4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-ylidene]acetate, 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-thienyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine and 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(tert-butyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine, optionally in the form of the racemates, enantiomers or diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof.

Particularly preferably the PDE4-inhibitor is selected from among enprofyllin, roflumilast, ariflo (cilomilast), arofyllin, atizoram, AWD-12-281 (GW-842470), T-440, T-2585, PD-168787, V-11294A, C1-1018, CDC-801, D-22888, YM-58997, Z-15370, N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxybenzamide, cis[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid], 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl) cyclohexan-1-one, cis[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol], 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-thienyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine and 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(tert-butyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine, optionally in the form of the racemates, enantiomers or diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof.

By acid addition salts with pharmacologically acceptable acids which the above-mentioned PDE4-inhibitors might be in a position to form are meant, for example, salts selected from among the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate, preferably hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate.

LTD4-antagonists which may be used are preferably compounds selected from among montelukast, pranlukast, zafirlukast, MCC-847 (ZD-3523), MN-001, MEN-91507 (LM-1507), VUF-5078, VUF-K-8707, L-733321, 1-(((R)-(3-(2-(6,7-difluoro-2-quinolinyl)ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)phenyl)thio)methylcyclopropane-acetic acid, 1-(((1(R)-3(3-(2-(2,3-dichlorothieno[3,2-b]pyridin-5-yl)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl) phenyl)propyl)thio)methyl)cyclopropane-acetic acid and [2-[[2-(4-tert-butyl-2-thiazolyl)-5-benzofuranyl]oxymethyl] phenyl]acetic acid, optionally in the form of the racemates, enantiomers or diastereomers, optionally in the form of the pharmacologically acceptable acid addition salts and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.

Preferably the LTD4-antagonist is selected from among montelukast, pranlukast, zafirlukast, MCC-847 (ZD-3523), MN-001, MEN-91507 (LM-1507), VUF-5078, VUF-K-8707 and L-733321, optionally in the form of the racemates, enantiomers or diastereomers, optionally in the form of the pharmacologically acceptable acid addition salts and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.

Particularly preferably the LTD4-antagonist is selected from among montelukast, pranlukast, zafirlukast, MCC-847 (ZD-3523), MN-001 and MEN-91507 (LM-1507), optionally in the form of the racemates, enantiomers or diastereomers, optionally in the form of the pharmacologically acceptable acid addition salts and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.

By acid addition salts with pharmacologically acceptable acids which the LTD4-antagonists may be capable of forming are meant, for example, salts selected from among the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate, preferably

hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate. By salts or derivatives which the LTD4-antagonists may be capable of forming are meant, for example: alkali metal salts, such as, for example, sodium or potassium salts, alkaline earth metal salts, sulphobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates.

The EGFR-inhibitors used are preferably compounds selected from among 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino}-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N, N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidin, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N, N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline, 4-{[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]amino}-6-(5-{[(2-methanesulphonyl-ethyl)amino]methyl}-furan-2-yl) quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis-(2-methoxy-ethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methane-sulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(methoxymethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-((S)-tetrahydrofuran-3-yloxy)-7-hydroxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(dimethylamino) sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-acetylamino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methanesulphonylamino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-aminocarbonylmethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(tetrahydropyran-4-yl) carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl) sulphonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-ethoxy-

quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-acetylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(4-methyl-piperazin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-isopropyloxycarbonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[N-(2-methoxy-acetyl)-N-methyl-amino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(cis-2,6-dimethyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(S,S)-(2-oxa-5-aza-bicyclo[2,2,1]hept-5-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(3-methoxypropyl-amino)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, Cetuximab, Trastuzumab, ABX-EGF and Mab ICR-62, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts, the solvates and/or hydrates thereof.

Preferred EGFR inhibitors are selected from among 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]

pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline, 4-{[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]amino}-6-(5-{[(2-methanesulphonyl-ethyl)amino]methyl}-furan-2-yl)quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis-(2-methoxy-ethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(tert.-butyloxy-carbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(methoxymethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-((S)-tetrahydrofuran-3-yloxy)-7-hydroxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(dimethylamino)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-acetylamino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methanesulphonylamino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-aminocarbonylmethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(tetrahydropyran-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)sulphonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-acetylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(4-methyl-piperazin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-isopropyloxycarbonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[N-(2-methoxy-acetyl)-N-methyl-amino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(cis-2,6-dimethyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(S,S)-(2-oxa-5-aza-bicyclo[2,2,1]hept-5-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(3-methoxypropyl-amino)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-

quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl) methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl) amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, and Cetuximab, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts, the solvates and/or hydrates thereof.

It is particularly preferable within the scope of the present invention to use those EGFR-inhibitors which are selected from among 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl) amino]-6-{[4((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl) amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl] amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(R)-(1-phenyl-ethyl) amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d] pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl] amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl] amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl) carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl) amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl) carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl) methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl) amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, and 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxy-ethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts, the solvates and/or hydrates thereof.

Particularly preferred EGFR-inhibitors according to the invention are the compounds selected from among 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-

N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline and 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts, the solvates and/or hydrates thereof.

By acid addition salts with pharmacologically acceptable acids which the EGFR-inhibitors may be capable of forming are meant, for example, salts selected from among the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate, preferably hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate.

Examples of dopamine agonists which may be used preferably include compounds selected from among bromocriptine, cabergoline, alpha-dihydroergocryptine, lisuride, pergolide, pramipexol, roxindol, ropinirol, talipexol, terguride and viozan. Any reference to the above-mentioned dopamine agonists within the scope of the present invention includes a reference to any pharmacologically acceptable acid addition salts and optionally hydrates thereof which may exist. By the physiologically acceptable acid addition salts which may be formed by the above-mentioned dopamine agonists are meant, for example, pharmaceutically acceptable salts which are selected from the salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid and maleic acid.

Examples of H1-antihistamines preferably include compounds selected from among epinastine, cetirizine, azelastine, fexofenadine, levocabastine, loratadine, mizolastine, ketotifen, emedastine, dimetinden, clemastine, bamipin, cexchlorpheniramine, pheniramine, doxylamine, chlorophenoxamine, dimenhydrinate, diphenhydramine, promethazine, ebastine, desloratidine and meclozine. Any reference to the above-mentioned H1-antihistamines within the scope of the present invention includes a reference to any pharmacologically acceptable acid addition salts which may exist.

Examples of PAF-antagonists preferably include compounds selected from among 4-(2-chlorophenyl)-9-methyl-2-[3(4-morpholinyl)-3-propanon-1-yl]-6H-thieno-[3,24]-[1,2,4]triazolo[4,3-a][1,4]diazepines, 6-(2-chlorophenyl)-8,9-dihydro-1-methyl-8-[(4-morpholinyl)carbonyl]-4H,7H-cyclo-penta-[4,5]thieno-[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepines.

MRP4-inhibitors used are preferably compounds selected from among N-acetyl-dinitrophenyl-cysteine, cGMP, cholate, diclofenac, dehydroepiandrosterone 3-glucuronide, dehydroepiandrosterone 3-sulphate, dilazep, dinitrophenyl-s-glutathione, estradiol 17-β-glucuronide, estradiol 3,17-disulphate, estradiol 3-glucuronide, estradiol 3-sulphate, estrone 3-sulphate, flurbiprofen, folate, N5-formyl-tetrahydrofolate, glycocholate, clycolithocholic acid sulphate, ibuprofen, indomethacin, indoprofen, ketoprofen, lithocholic acid sulphate, methotrexate, MK571 ((E)-3-[[[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-[[3-dimethylamino)-3-oxopropyl]thio]methyl]thio]-propanoic acid), α-naphthyl-β-D-glucuronide, nitrobenzyl mercaptopurine riboside, probenecid, PSC833, sildenafil, sulfinpyrazone, taurochenodeoxycholate, taurocholate, taurodeoxycholate, taurolithocholate, taurolithocholic acid sulphate, topotecan,

trequinsin and zaprinast, dipyridamole, optionally in the form of the racemates, enantiomers, diastereomers and the pharmacologically acceptable acid addition salts and hydrates thereof.

Preferably the invention relates to the use of MRP4-inhibitors for preparing a pharmaceutical composition for the treatment of respiratory complaints, containing the PDE4B-inhibitors and MRP4-inhibitors, the MRP4-inhibitors preferably being selected from among N-acetyl-dinitrophenyl-cysteine, dehydroepiandrosterone 3-sulphate, dilazep, dinitrophenyl-S-glutathione, estradiol 3,17-disulphate, flurbiprofen, glycocholate, glycolithocholic acid sulphate, ibuprofen, indomethacin, indoprofen, lithocholic acid sulphate, MK571, PSC833, sildenafil, taurochenodeoxycholate, taurocholate, taurolithocholate, taurolithocholic acid sulphate, trequinsin and zaprinast, dipyridamole, optionally in the form of the racemates, enantiomers, diastereomers and the pharmacologically acceptable acid addition salts and hydrates thereof.

The invention relates more preferably to the use of MRP4-inhibitors for preparing a pharmaceutical composition for treating respiratory complaints, containing the PDE4B-inhibitors and MRP4-inhibitors according to the invention, the MRP4-inhibitors preferably being selected from among dehydroepiandrosterone 3-sulphate, estradiol 3,17-disulphate, flurbiprofen, indomethacin, indoprofen, MK571, taurocholate, optionally in the form of the racemates, enantiomers, diastereomers and the pharmacologically acceptable

acid addition salts and hydrates thereof. The separation of enantiomers from the racemates can be carried out using methods known from the art (e.g. chromatography on chiral phases, etc.).

By acid addition salts with pharmacologically acceptable acids are meant, for example, salts selected from among the hydrochlorides, hydrobromides, hydroiodides, hydrosulphates, hydrophosphates, hydromethanesulphonates, hydronitrates, hydromaleates, hydroacetates, hydrobenzoates, hydrocitrates, hydrofumarates, hydrotartrates, hydrooxalates, hydrosuccinates, hydrobenzoates and hydrop-toluenesulphonates, preferably the hydrochlorides, hydrobromides, hydrosulphates, hydrophosphates, hydrofumarates and hydromethanesulphonates.

The invention further relates to pharmaceutical preparations which contain a triple combination of the PDE4B-inhibitors, MRP4-inhibitors and another active substance according to the invention, such as, for example, an anticholinergic, a steroid, an LTD4-antagonist or a betamimetic, and the preparation thereof and the use thereof for treating respiratory complaints.

The iNOS-inhibitors used are preferably compounds selected from among: S-(2-aminoethyl)isothiourea, aminoguanidine, 2-aminomethylpyridine, AMT, L-canavanine, 2-iminopiperidine, S-isopropylisothiourea, S-methylisothiourea, S-ethylisothiourea, S-methyltiocitrulline, S-ethylthiocitrulline, L-NA (N^{ω}-nitro-L-arginine), L-NAME (N^{ω}-nitro-L-arginine methylester), L-NMMA (N^{G}-monomethyl-L-arginine), L-NIO (N^{ω}-iminoethyl-L-ornithine), L-NIL (N^{ω}-iminoethyl-lysine), (S)-6-acetimidoylamino-2-aminohexanoic acid (1H-tetrazol-5-yl)-amide (SC-51) (*J. Med. Chem.* 2002, 45, 1686-1689), 1400W, (S)-4-(2-acetimidoylamino-ethylsulphanyl)-2-amino-butyric acid (GW274150) (*Bioorg. Med. Chem. Lett.* 2000, 10, 597-600), 2-[2-(4-methoxy-pyridin-2-yl)-ethyl]-3H-imidazo[4,5-b]pyridine (BYK191023) (*Mol. Pharmacol.* 2006, 69, 328-337), 2-((R)-3-amino-1-phenyl-propoxy)-4-chloro-5-fluorobenzonitrile (WO 01/62704), 2-((1R.3S)-3-amino-4-hydroxy-1-thiazol-5-yl-butylsulphanyl)-6-trifluoromethyl-nicotinonitrile (WO 2004/041794), 2-((1R.3S)-3-amino-4-hydroxy-1-thiazol-5-yl-butylsulphanyl)-4-chloro-benzonitrile (WO 2004/041794), 2-((1R.3S)-3-amino-4-hydroxy-1-thiazol-5-yl-butylsulphanyl)-5-chloro-benzonitrile (WO 2004/041794), (2S,4R)-2-amino-4-(2-chloro-5-trifluoromethyl-phenylsulphanyl)-4-thiazol-5-yl-butan-1-ol (WO 2004/041794), 2-((1R.3S)-3-amino-4-hydroxy-1-thiazol-5-yl-butylsulphanyl)-5-chloro-nicotinonitrile (WO 2004/041794), 4-((S)-3-amino-4-hydroxy-1-phenyl-butylsulphanyl)-6-methoxy-nicotinonitrile (WO 02/090332), substituted 3-phenyl-3,4-dihydro-1-isoquinolinamines such as e.g. AR-C102222 (*J. Med. Chem.* 2003, 46, 913-916), (1S.5S.6R)-7-chloro-5-methyl-2-aza-bicyclo[4.1.0]hept-2-en-3-ylamine (ONO-1714) (*Biochem. Biophys. Res. Commun.* 2000, 270, 663-667), (4R.5R)-5-ethyl-4-methyl-thiazolidin-2-ylideneamine (*Bioorg. Med. Chem.* 2004, 12, 4101), (4R.5R)-5-ethyl-4-methyl-selenazolidin-2-ylideneamine (*Bioorg. Med. Chem. Lett.* 2005, 15, 1361), 4-aminotetrahydrobiopterine (*Curr. Drug Metabol.* 2002, 3, 119-121), (E)-3-(4-chloro-phenyl)-N-(1-{2-oxo-2-[4-(6-trifluoromethyl-pyrimidin-4-yloxy)-piperidin-1-yl]-ethylcarbamoyl}-2-pyridin-2-yl-ethyl)-acrylamide (FR260330) (*Eur. J. Pharmacol.* 2005, 509, 71-76), 3-(2,4-difluoro-phenyl)-6-[2-(4-imidazol-1-ylmethyl-phenoxy)-ethoxy]-2-phenyl-pyridine (PPA250) (*J. Pharmacol. Exp. Ther.* 2002, 303, 52-57), methyl 3-{[(benzo[1.3]dioxol-5-ylmethyl)-carbamoyl]-methyl}-4-(2-imidazol-1-yl-pyrimidin-4-yl)-piperazin-1-carboxylate (BBS-1) (*Drugs Future* 2004, 29, 45-52), (R)-1-(2-imidazol-1-yl-6-methyl-pyrimidin-4-yl)-pyrrolidine-2-carboxylic acid (2-benzo[1.3]dioxol-5-yl-ethyl)-amide (BBS-2) (*Drugs Future* 2004, 29, 45-52) and the pharmaceutical salts, prodrugs or solvates thereof.

Other iNOS-inhibitors which may be used within the scope of the present invention are antisense oligonucleotides, particularly antisense oligonucleotides that bind iNOS-coding nucleic acids. For example, WO 01/52902 describes antisense oligonucleotides, particularly antisense-oligonucleotides, which bind iNOS-coding nucleic acids, for modulating the expression of iNOS. Those iNOS-antisense-oligonucleotides as described particularly in WO 01/52902 may therefore also be combined with the PDE4-inhibitors of the present invention on the basis of their similar activity to the iNOS inhibitors.

Compounds which may be used as SYK-inhibitors are preferably compounds selected from among: R343 or R788.

Pharmaceutical Formulations

Suitable forms for administration are for example tablets, capsules, solutions, syrups, emulsions or inhalable powders or aerosols. The content of the pharmaceutically effective compound(s) in each case should be in the range from 0.1 to 90 wt. %, preferably 0.5 to 50 wt. % of the total composition, i.e. in amounts which are sufficient to achieve the dosage range specified hereinafter.

The preparations may be administered orally in the form of a tablet, as a powder, as a powder in a capsule (e.g. a hard gelatine capsule), as a solution or suspension. When administered by inhalation the active substance combination may be given as a powder, as an aqueous or aqueous-ethanolic solution or using a propellant gas formulation.

Preferably, therefore, pharmaceutical formulations are characterised in that they contain one or more compounds of formula I according to the preferred embodiments above.

It is particularly preferable if the compounds of formula I are administered orally, and it is also particularly preferable if they are administered once or twice a day. Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolins, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates), sugars (e.g. cane sugar, lactose and glucose), emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

For oral administration the tablets may, of course, contain, apart from the abovementioned carriers, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additives such as starch, preferably potato starch, gelatine and the like. Moreover, lubricants such as magnesium stearate, sodium lauryl sulphate and talc may be used at the same time for the tabletting process. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the excipients mentioned above.

It is also preferred if the compounds of formula I are administered by inhalation, particularly preferably if they are administered once or twice a day. For this purpose, the compounds of formula I have to be made available in forms suitable for inhalation. Inhalable preparations include inhalable powders, propellant-containing metered-dose aerosols or propellant-free inhalable solutions, which are optionally present in admixture with conventional physiologically acceptable excipients.

Within the scope of the present invention, the term propellant-free inhalable solutions also includes concentrates or sterile ready-to-use inhalable solutions. The preparations which may be used according to the invention are described in more detail in the next part of the specification.

Inhalable Powders

If the active substances of formula I are present in admixture with physiologically acceptable excipients, the following physiologically acceptable excipients may be used to prepare the inhalable powders according to the invention: monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose), oligo- and polysaccharides (e.g. dextran), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or disaccharides are used, while the use of lactose or glucose is preferred, particularly, but not exclusively, in the form of their hydrates. For the purposes of the invention, lactose is the particularly preferred excipient, while lactose monohydrate is most particularly preferred. Methods of preparing the inhalable powders according to the invention by grinding and micronising and by finally mixing the components together are known from the prior art.

Propellant-Containing Inhalable Aerosols

The propellant-containing inhalable aerosols which may be used according to the invention may contain 1 dissolved in the propellant gas or in dispersed form. The propellant gases which may be used to prepare the inhalation aerosols according to the invention are known from the prior art. Suitable propellant gases are selected from among hydrocarbons such as n-propane, n-butane or isobutane and halohydrocarbons such as preferably fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane. The propellant gases mentioned above may be used on their own or in mixtures thereof. Particularly preferred propellant gases are fluorinated alkane derivatives selected from TG134a (1,1,1,2-tetrafluoroethane), TG227 (1,1,1,2,3,3,3-heptafluoropropane) and mixtures thereof. The propellant-driven inhalation aerosols used within the scope of the use according to the invention may also contain other ingredients such as co-solvents, stabilisers, surfactants, antioxidants, lubricants and pH adjusters. All these ingredients are known in the art.

Propellant-Free Inhalable Solutions

The compounds of formula I according to the invention are preferably used to prepare propellant-free inhalable solutions and inhalable suspensions. Solvents used for this purpose include aqueous or alcoholic, preferably ethanolic solutions. The solvent may be water on its own or a mixture of water and ethanol. The solutions or suspensions are adjusted to a pH of 2 to 7, preferably 2 to 5, using suitable acids. The pH may be adjusted using acids selected from inorganic or organic acids. Examples of particularly suitable inorganic acids include hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid and/or phosphoric acid. Examples of particularly suitable organic acids include ascorbic acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid and/or propionic acid etc. Preferred inorganic acids are hydrochloric and sulphuric acids. It is also possible to use the acids which have already formed an acid addition salt with one of the active substances. Of the organic acids, ascorbic acid, fumaric acid and citric acid are preferred. If desired, mixtures of the above acids may also be used, particularly in the case of acids which have other properties in addition to their acidifying qualities, e.g. as flavourings, antioxidants or complexing agents, such as citric acid or ascorbic acid, for example. According to the invention, it is particularly preferred to use hydrochloric acid to adjust the pH. Co-solvents and/or other excipients may be added to the propellant-free inhalable solutions used for the purpose according to the invention. Preferred co-solvents are those which contain hydroxyl groups or other polar groups, e.g. alcohols—particularly isopropyl alcohol, glycols—particularly propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycolether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters. The terms excipients and additives in this context denote any pharmacologically acceptable substance which is not an active substance but which can be formulated with the active substance or substances in the pharmacologically suitable solvent in order to improve the qualitative properties of the active substance formulation. Preferably, these substances have no pharmacological effect or, in connection with the desired therapy, no appreciable or at least no undesirable pharmacological effect. The excipients and additives include, for example, surfactants such as soya lecithin, oleic acid, sorbitan esters, such as polysorbates, polyvinylpyrrolidone, other stabilisers, complexing agents, antioxidants and/or preservatives which guarantee or prolong the shelf life of the finished pharmaceutical formulation, flavourings, vitamins and/or other additives known in the art. The additives also include pharmacologically acceptable salts such as sodium chloride as isotonic

agents. The preferred excipients include antioxidants such as ascorbic acid, for example, provided that it has not already been used to adjust the pH, vitamin A, vitamin E, tocopherols and similar vitamins or provitamins occurring in the human body. Preservatives may be used to protect the formulation from contamination with pathogens. Suitable preservatives are those which are known in the art, particularly cetyl pyridinium chloride, benzalkonium chloride or benzoic acid or benzoates such as sodium benzoate in the concentration known from the prior art. For the treatment forms described above, ready-to-use packs of a medicament for the treatment of respiratory complaints are provided, containing an enclosed description including for example the words respiratory disease, COPD or asthma, a pteridine and one or more combination partners selected from those described above.

EXPERIMENTAL PROCEDURES AND SYNTHETIC EXAMPLES

List of Abbreviations

ACN acetonitrile
APCI atmospheric pressure chemical ionization (in MS)
Ctrl control
DAD diode array detector
DMA N,N-dimethylacetamide'
DMF N,N-dimethylformamide
DMSO dimethyl sulfoxide
EI electron impact (in MS)
ESI electrospray ionization (in MS)
ex example
GC/MS gas chromatography with mass spectrometric detection
h hour(s)
HATU O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-phosphate
HPLC high performance liquid chromatography
HPLC/MS coupled high performance liquid chromatography-mass spectrometry
min minutes
MS mass spectrometry
NMR nuclear magnetic resonance
R_t retention time (in HPLC)
sec secondary
TBTU O-(1H-benzo-1,2,3-triazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
tert tertiary
TFA trifluoroacetic acid
TLC thin-layer chromatography
UV ultraviolet absorption
Analytical Methods
HPLC Methods
Methods:
1A
Column: Sunfire MS-C8, 5 μm, 4.6×100 mm
Mobile phase: A=(10 nM aqueous solution of NH_4COOH)+10% ACN;
B=ACN+10% (10 nM aqueous solution of NH_4COOH).
Flow rate: 1500 μL/min
Gradient: A/B (95/5%) for 1 min then to A/B (5/95%) in 10 min for 2 min
1E
Column: Symmetry C8, 5 μm, 3×150 mm
Mobile phase: A=(10 nM aqueous solution of NH_4COOH)+10% ACN;
B=ACN+10% (10 nM aqueous solution of NH_4COOH).
Flow rate: 1200 μL/min
Gradient: A (100%) for 1.5 min then to B (100%) in 10 min for 3 min
1E (Fusion)
Column: Synergy Fusion RP80A, 4 μm, 4.6×100 mm
Mobile phase: A=(10 nM aqueous solution of NH_4COOH)+10% ACN;
B=ACN+10% (10 nM aqueous solution of NH_4COOH).
Flow rate: 1200 μL/min
Gradient: A (100%) for 1.5 min then to B (100%) in 10 min for 3 min
1E (Hydro)
Column: Synergy Hydro RP80A, 4 μm, 4.6×100 mm
Mobile phase: A=(10 nM aqueous solution of NH_4COOH)+10% ACN;
B=ACN+10% (10 nM aqueous solution of NH_4COOH).
Flow rate: 1200 μL/min
Gradient: A (100%) for 1.5 min then to B (100%) in 10 min for 3 min
Equipment:
Instrument: HPLC/MS ThermoFinnigan HPLC Surveyor DAD,
Detection: UV @ 254 nm
Detection: Finnigan MSQ, quadrupole
Ion source: APCI
Method:
1F
Column: Xterra MS-C8, 3.5 μm, 4.6×50 mm
Mobile phase: A=(H_2O+0.1% TFA)+10% ACN; B=ACN
Flow rate: 1300 μL/min
Gradient: A (100%) then to A/B (10/90%) in 3.25 min for 0.75 min
1Fa
Column: Xterra MS-C18, 5 μm, 4.6×50 mm
Mobile phase: A=(H_2O+0.1% NH4COOH)+10% ACN; B=ACN
Flow rate: 1300 μL/min
Gradient: A (100%) then to A/B (10/90%) in 3.25 min for 0.75 min
Equipment:
Instrument: HPLC/MS Waters. Hplc Alliance 2695 DAD, ZQ Quadrupole
Detection: UV @ 254 nm
Detection: Waters ZQ, Quadrupole;
Ion source: ESI
Methods:
2A
Column: X-Terra MS C18 4.6×50 mm, 3.5 μm;
Column Temperature: 40.0° C.
Mobile phase: A=H_2O+0.1% TFA; B=ACN+0.1% TFA
Flow rate: 1500 μL/min

Gradient:

Time	A %	B %
0.00	95.00	5.00
2.00	0.00	100.00
2.49	0.00	100.00
2.50	95.00	5.00

2B
Column: X-Terra MS C18 4.6×50 mm, 3.5 μm;
Column Temperature: 40.0° C.
Mobile phase: A=H_2O+0.1% TFA; B=ACN+0.1% TFA
Flow rate: 1000 μL/min

Gradient:		
Time	A %	B %
0.00	95.00	5.00
0.40	95.00	5.00
4.00	2.00	98.00
4.35	2.00	98.00
4.50	95.00	5.00

2C
Column: Sunfire C18 4.6×50 mm, 3.5 μm;
Column Temperature: 40.0° C.
Mobile phase: A=H_2O+0.1% TFA; B=ACN+0.1% TFA
Flow rate: 1500 μL/min

Gradient:		
Time:	A %	B %
0.00	95.00	5.00
2.00	0.00	100.00
2.49	0.00	100.00
2.50	95.00	5.00

Equipment
Instrument: Waters ZQ2000 mass spectrometer
Detection: HP1100 HPLC+DAD (Wavelength range: 210 to 500 nM)+Gilson 215 Autosampler
Ion source: ESI+
Method:
2Ca
Column: MERCK; Chromolith Flash; RP18e; 25×4.6 mm
Mobile phase: A=water+0.1% HCOOH; B=ACN+0.1% HCOOH
Flow rate: 1.6 ml/min

Gradient:		
A %	B %	Time [min]
90	10	0.00
10	90	2.70
10	90	3.00
90	10	3.30

2Cb
Column: MERCK; Chromolith Flash; RP18e; 25×4.6 mm
Mobile: A=water+0.1% HCOOH; B=MeOH
Flow rate: 1.6 ml/min

Gradient:		
A %	B %	Time [min]
90	10	0.00
0	100	2.50
0	100	3.50

Equipment
Instrument: Agilent Technology; HP 1200 Series, DAD SL
Detection: UV 240-254 nm
Detection: Waters ZQ Single Quad
Ion source: ESI+
Method:
2F
Column: Symmetry Shield RP8, 5 μm, 4.6×150 mm
Mobile phase: A=(H_2O+HCOOH 0.1%)+10% ACN
B=ACN+10% (H_2O+0.1% HCOOH)
Flow rate: 1000 μL/min
Gradient: A/B (95/5%) for 1.5 min then to A/B (5/95%) in 10 min for 1.5 min
2M
Column: Symmetry Shield RP8, 5 μm, 4.6×150 mm
Mobile phase: A=(H_2O+HCOOH 0.1%)+10% ACN
B=ACN+10% (H_2O+0.1% HCOOH)
Flow rate: 1200 μL/min
Gradient: A/B (90/10%) for 1.5 min then to A/B (5/95%) in 10 min for 2 min
Equipment:
Instrument: HPLC/MS ThermoFinnigan HPLC Surveyor DAD, LCQDuo Ion Trap
Detection: UV λ54 nm
Detection: Finnigan LCQDuo Ion Trap
Ion source: ESI
Method:
2G
Eluent: A=H2O+0.05% TFA; B=ACN
Column: Waters SunFire C18 30×100 mm 5 μm

Gradient:	slope 5%/min		
Initial:	Flow = 40 mL/min	% A = 80	% B = 20
8 min	Flow = 40 mL/min	% A = 40	% B = 60
9 min	Flow = 40 mL/min	% A = 40	% B = 60
10 min	Flow = 40 mL/min	% A = 5	% B = 95
11 min	Flow = 40 mL/min	% A = 5	% B = 95
11.5 min	Flow = 40 mL/min	% A = 80	% B = 20
Stop run after 12 min Pre-run method: Initial condition for 3 min			

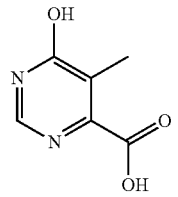
Equipment:

Detector MS Waters ZQ:		Detector DAD Waters 996:	
File:	APrep_ESI.ipr	Start Wavelength:	210 nm
Polarity:	ESI+	End Wavelength:	600 nm
Mass range:	130 to 900 amu	Resolution:	1.2 nm
		Sampling rate:	1 spectra/sec
Sample Manager mod Waters 2767:		**Make up pump mod Waters 515:**	
Injection type:	partial loop	Flow =	1000 μL/min
Injection Volume:	set to Open Access Login mask	Solvent =	ACN/Water/Formic acid (90/10/0.1)
Syringe size:	5000 uL	Splitter:	1:1000
Trigger:	mixed Total scan UV plus MS A		
Loop Volume:	5000 uL		

Method:
2Ga
Column: BEH C18, 1.8 um, 2.1×100 mm
Mobile phase: A=(H_2O+NH4COOH 0.1%)
B=ACN+10% H_2O
Flow rate: 450 μL/min
Gradient: 100% A for 1.5 min then to 100% B in 2.2 min
2Gb
Column: BEH C18, 1.7 um, 2.1×50 mm
Mobile phase: A=H_2O 90%+0.1% TFA+10% ACN
B=ACN+10% H_2O
Flow rate: 480 μL/min
Gradient: A/B (90:10), then to A/B (10:90) in 1.2 minutes for 0.46 minute
Equipment:
Instrument: UPLC/MS AcquityWaters
Detection: UV λ254 nm
Detection: Waters SQD, Quadrupole
Ion source: ESI
Method:
2H (Isocratic)
Column: DAICEL (IC) 5 μm, 4.6×250 mm
Mobile phase: A=(hexane+0.2% diethylamine); B=(MeOH/EtOH 50/50%).
A/B=50/50%
Flow rate: 1 ml/min
2I (Isocratic)
Column: DAICEL AS-H 5 μm, 4.6×250 mm
Mobile phase: A=Hexane; B=EtOH (con AS-H), IPA (con AD-H)
A/B=98/2%
Flow rate: 1 ml/min
Equipment
Instrument: LC Agilent Technologies. HPLC 1100 Serie, DAD Version A.
Detection: UV 220-300 nm
GC-MS Methods:
Method:
3A
Column: Agilent DB-5MS, 25 m×0.25 mm×0.25 μm
Carrier gas: Helium, 1 ml/min costant flow
Oven Program: 50° C. (hold 1 min), to 100° C. in 10° C./min, to 200° C. in 20° C./min, to 300° C. in 30° C./min
Equipment
Instrument: GC/MS Finnigan TRACE GC, TRACE MS quadrupole
Detection: TRACE MS quadrupole
Ion source: EI
Microwave Heating:
Discover® CEM instruments, equipped with 10 and 35 mL vessels.

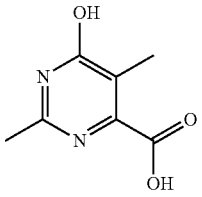
SYNTHESIS OF INTERMEDIATES

Intermediate 1a



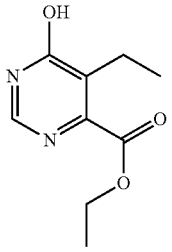
Potassium hydroxide (37.9 g, 0.67 mol) was suspended in 200 ml of dry ethanol, formamidine acetate (28.1 g, 0.27 mol) and diethyl oxalpropionate (50 ml, 0.27 mol) were added and the reaction mixture was stirred under reflux overnight. The reaction mixture was cooled to room temperature and the precipitate formed was filtered, washed with ethanol and diethyl ether, dissolved in 200 ml of water and the solution obtained acidified by a 37% aqueous solution of hydrochloric acid until pH=2. The acidic aqueous solution was concentrated under vacuum and the residue obtained was suspended and stirred in 100 ml of methanol. The insoluble inorganic salts were filtered off. The solution was concentrated. 15 g (97.4 mmol) of the desired compound were obtained.

Intermediate 1b



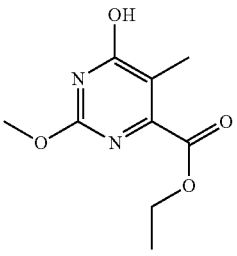
was synthesized in analogy to Intermediate 1a, starting from acetamidine hydrochloride.

Intermediate 1c



Potassium-tert-butylate (185.4 g, 1.65 mol) was dissolved in 650 ml of dry ethanol and added slowly at −10° C. to a suspension of 2-ethyl-3-oxo-succinic-acid diethyl ester (274.3 g, 1.27 mol) and formamidine acetate (171.4 g, 1.65 mol). The reaction mixture was stirred at room temperature overnight, concentrated in vacuum and ice water was added. The mixture was acidified by a 37% aqueous solution of hydrochloric acid until pH=5 and extracted with chloroform. After drying the organic layer, evaporation of the solvent in vacuum and crystallization from ethyl acetate/hexane (2:3) gave 38 g (0.19 mol) of the desired compound.

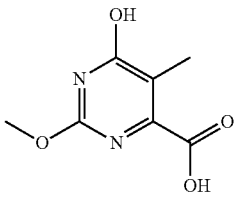
Intermediate 1d



A suspension of sodium tert-butoxide (3.9 g, 40.5 mmol) in 25 ml dry ethanol was added to a solution of diethyl oxalpro-

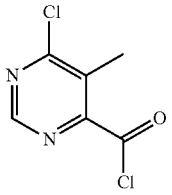
pionate (3.0 ml, 16.2 mmol) and O-methylisourea hydrochloride (2.15 g, 19.5 mmol) in 25 ml dry ethanol and the reaction mixture was refluxed for 18 h. The reaction mixture was allowed to cool to room temperature and the precipitate removed by filtration. The filtrate was concentrated in vacuum, and the residue was purified by reversed phase HPLC to give the desired product (752 mg, 3.5 mmol).

Intermediate 1e



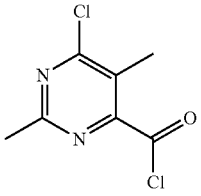
Intermediate 1d (550 mg, 2.6 mmol) was dissolved in a 4 M aqueous solution of sodium hydroxide (3.0 ml, 12.0 mmol) and stirred for 3 h at room temperature. The reaction mixture was acidified with concentrated hydrochloric acid to yield the desired product as precipitate (443 mg, 2.4 mmol).

Intermediate 2a



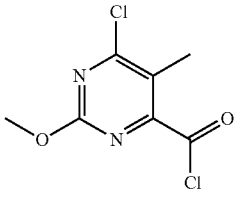
Intermediate 1a (7.0 g, 45.4 mmol) was suspended in 35 ml of thionyl chloride (0.45 mol), 0.10 ml of DMF was added and the reaction mixture was refluxed for 1 h. The reaction mixture was concentrated in vacuum. 8.6 g (45 mmol) of the desired product were obtained and used in the next steps without further purification.

Intermediate 2b



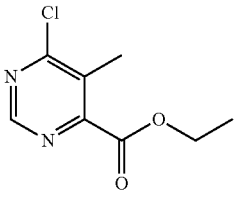
was synthesized in analogy to Intermediate 2a, starting from Intermediate 1b.

Intermediate 2c



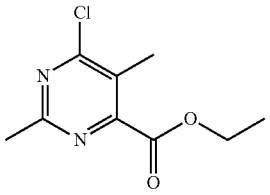
was synthesized in analogy to Intermediate 2a, starting from Intermediate 1e.

Intermediate 3a



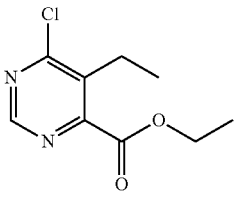
Potassium carbonate (43.34 g, 0.31 mol) was suspended in 350 ml of dry ethanol. A solution of Intermediate 2a (20 g, 0.10 mol) in 10 ml of dichloromethane was added slowly at 0° C. The reaction mixture was allowed to reach room temperature and stirred for 1 h. Potassium carbonate was filtered off and the solvent was removed under vacuum. The crude product was purified by flash chromatography (BIOTAGE SP1; silica gel cartridge: 65i; eluent: dichloromethane/ethyl acetate=95/5%). 5.3 g (26 mmol) of the desired compound were obtained.

Intermediate 3b



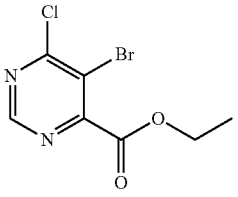
was synthesized in analogy to Intermediate 3a, starting from Intermediate 2b.

Intermediate 3c



Intermediate 1c (38 g, 0.19 mol) was added to a mixture of phosphorpentachloride (40.3 g, 0.19 mol) in 240 ml of phosphoroxychloride. The reaction mixture was refluxed until a clear solution was observed. The reaction mixture was concentrated in vacuum. The crude product obtained was purified by distillation in vacuum. 12 g (94.5 mmol) of the desired compound were obtained and used in the next steps without further purification.

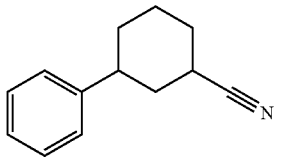
Intermediate 3d



5-Bromo-6-hydroxy-pyrimidine-4-carboxylic acid ethyl ester (63 g, 0.26 mol) was suspended in 140 ml of phos-

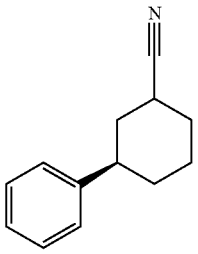
phoroxychloride. Phosphorpentachloride (54 g, 0.26 mmol) was added and the reaction mixture was refluxed 72 h. The reaction mixture was concentrated in vacuum and the crude product was suspended and stirred in warmed-up hexane (50° C.); a precipitate was formed and filtered off. The filtrate was concentrated under vacuum to obtain 64 g (243 mmol) of the desired product which was used in the next steps without further purification.

Intermediate 4a



3-Phenylcyclohexanone (500 mg, 2.87 mmol) and 1-isocyanomethanesulfonyl-4-methyl-benzene (750 mg, 3.84 mmol) in 10 ml of 1,2-dimethoxyethane were stirred at 0° C. A solution of potassium tert-butoxide (650 mg, 5.79 mmol) in 10 ml of 1,2-dimethoxyethane and 20 ml of tert-butanol was added dropwise and the reaction mixture was allowed to reach room temperature and stirred overnight. The reaction mixture was diluted with diethyl ether and washed with ice water. The organic phase was separated, washed with brine, dried over sodium sulfate and concentrated under vacuum. 439 mg (2.3 mmol) of the desired product were obtained.

Intermediate 4b

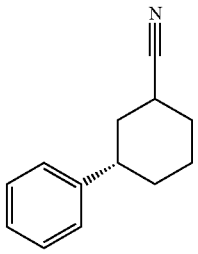


was synthesized in analogy to Intermediate 4a, starting from (R)-3-Phenylcyclohexanone.

GC/MS (method 3A) R_t=11.52 min and 11.68 min (diastereoisomeric mixture)

$[M]^+$=185

Intermediate 4c

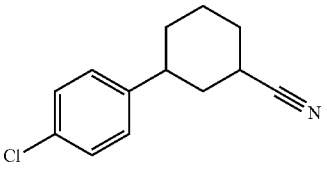
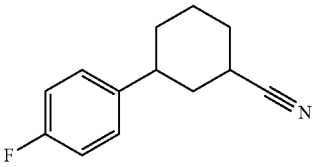
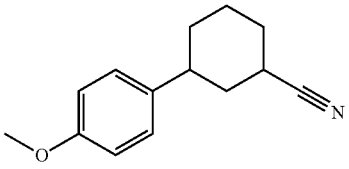
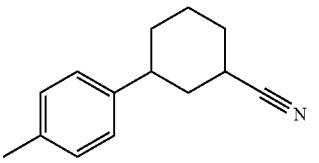
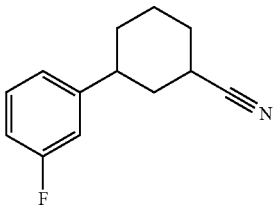
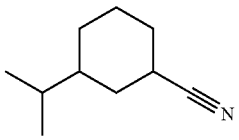
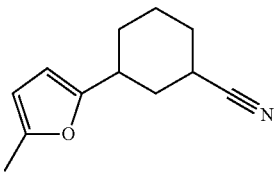
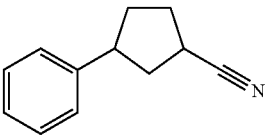


was synthesized in analogy to Intermediate 4a, starting from (S)-3-Phenylcyclohexanone.

GC/MS (method 3A) R_t=11.50 min and 11.65 min (diastereoisomeric mixture)

$[M]^+$=185

The following intermediates were synthesized in analogy to Intermediates 4a.

Starting ketone	Intermediate	STRUCTURE
3-(4-Chloro-phenyl)-cyclohexanone	4d	
3-(4-Fluoro-phenyl)-cyclohexanone	4e	
3-(4-Methoxy-phenyl)-cyclohexanone	4f	
3-(4-Methyl-phenyl)-cyclohexanone	4g	
3-(3-Fluoro-phenyl)-cyclohexanone	4h	
3-isopropyl-cyclohexanone	4i	
3-(5-Methyl-furan-2-yl)-cyclo-hexanone	4j	
3-Phenylcyclo-pentanone	4k	

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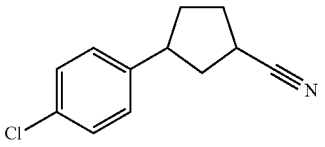
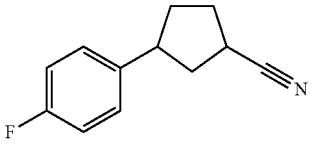
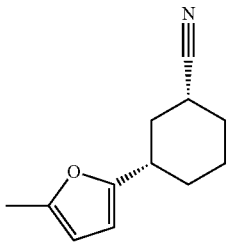
Starting ketone	Intermediate	STRUCTURE
3-(4-Chlorophenyl)-cyclopentanone	4l	
3-(4-Fluorophenyl)-cyclopentanone	4m	

Intermediate 4n

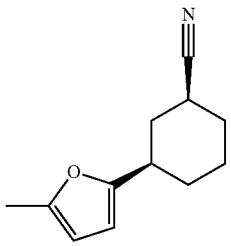


Intermediate 4j (400 mg, 2.11 mmol) was purified by flash chromatography (Biotage SP1 cartridge 25 g; eluent: cyclohexane/ethyl acetate=99/1%). 60 mg (0.22 mmol) of diastereoisomerically pure cis-intermediate was eluted as second fraction (relative stereochemistry assigned by NMR).

GC/MS (method 3A) R_t=9.62 min

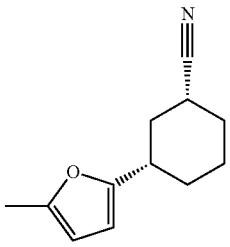
$[M]^+$=189

Intermediate 4o



Intermediate 4n (120 mg, 4.22 mmol) was separated by chiral semipreparative HPLC. 20 mg of enantiomerically pure intermediate 4o were obtained (absolute stereochemistry unknown). Chiral HPLC (method 2I (isocratic)) R_t=6.94 min

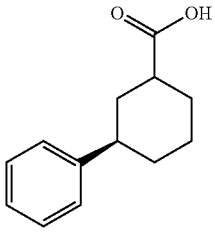
Intermediate 4p



Further elution of the column gave 20 mg of enantiomerically pure intermediate 4p (absolute stereochemistry unknown).

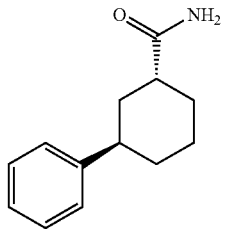
Chiral HPLC (method 2I (isocratic)) R_t=7.27

Intermediate 5



Intermediate 4b (2.1 g, 11.28 mmol) was stirred under reflux in 20 ml of 96% sulfuric acid and 20 ml of water overnight. The reaction mixture was cooled, treated with a 30% aqueous solution of sodium hydroxide and ice and washed with dichloromethane. The basic water phase was treated with 37% aqueous solution of hydrochloric acid. The acidic aqueous solution was extracted with dichloromethane. The organic phase was washed with brine, dried over sodium sulfate and concentrated under vacuum. 1.85 g (9.1 mmol) of the desired compound were obtained as a diastereoisomeric mixture and used in the next steps without further purification.

Intermediate 6a



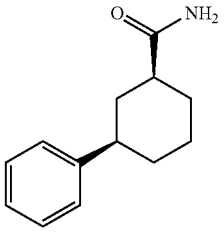
Intermediate 5 (1.85 g, 9.06 mmol, mixture of 2 diastereomers) and triethylamine (2.02 ml, 14 mmol) were stirred at 0° C. in 10 ml of tetrahydrofuran. A solution of ethylchloroformate (1.29 ml, 13.58 mmol) in 5 ml of tetrahydrofuran was added dropwise and the reaction mixture was stirred at 0° C. for 1 h. Then, 10 ml of a 30% aqueous solution of ammonium hydroxide were added dropwise and the reaction mixture was allowed to reach room temperature and stirred overnight. The reaction mixture was concentrated under vacuum, dissolved with dichloromethane, washed with a 1M aqueous solution of sodium hydroxide, washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Isolute silica cartridge

70 g; eluent: dichloromethane/methanol=99/1%). 145 mg (0.71 mmol) of diastereoisomerically pure (1R,3R)-3-phenyl-cyclohexanecarboxylic acid amide (relative stereochemistry assigned by NMR) were obtained.

GC/MS (method 3A) R_t=12.88 min

$[M]^+$=203

Intermediate 6b

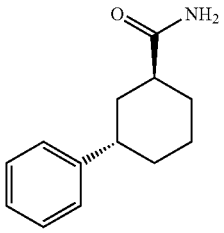


Further elution of the column gave 230 mg (1.13 mmol) of the diastereoisomerically pure (1S,3R)-3-phenyl-cyclohexanecarboxylic acid amide (relative stereochemistry assigned by NMR).

GC/MS (method 3A) R_t=13.03 min

$[M]^+$=203

Intermediate 6c

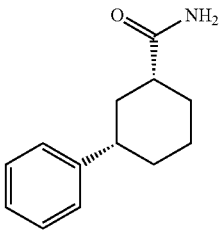


Intermediate 4c (300 mg, 1.61 mmol) was stirred under reflux in 2 ml of 96% sulfuric acid and 2 ml of water for 3 h. The reaction mixture was cooled, treated with a 30% aqueous solution of sodium hydroxide and ice and washed with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Isolute silica cartridge 20 g; eluent: dichloromethane/methanol=99/1%). 37 mg (0.18 mmol) of the diastereomerically pure (1S,3S)-3-phenyl-cyclohexanecarboxylic acid amide were obtained (relative stereochemistry assigned by NMR).

GC/MS (method 3A) R_t=12.88 min

$[M]^+$=203

Intermediate 6d

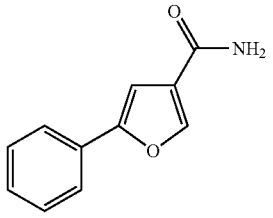


Further elution of the column gave 40 mg of the diastereomerically pure (1R,3S)-3-phenyl-cyclohexanecarboxylic acid amide (0.2 mmol) (relative stereochemistry assigned by NMR).

GC/MS (method 3A) R_t=13.03 min

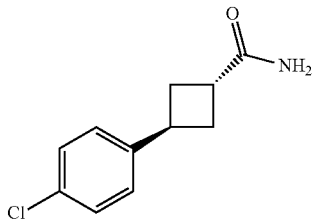
$[M]^+$=203

Intermediate 6e



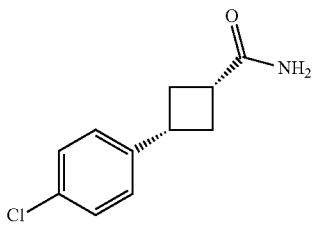
5-Bromo-3-furan carboxylic acid (1.0 g, 5.23 mmol), phenylboronic acid (0.77 g, 6.28 mmol), tetrakis(triphenylphosphine)palladium(0) (1.21 g, 1.04 mmol) and a 2M solution of sodium carbonate (6.28 ml, 12.57 mmol) were dissolved in 12 ml of 1,2-dimethoxy-ethane and the reaction mixture was stirred under nitrogen atmosphere at 80° C. for 18 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane and treated with a 1M aqueous solution of hydrochloric acid until pH 1. The organic phase was separated, dried over sodium sulphate and concentrated under vacuum. The carboxylic acid was obtained and used without further purification for the synthesis of intermediate 6e in analogy to intermediate 6a.

Intermediate 6f



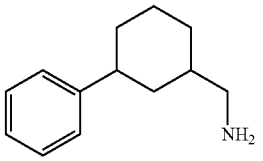
Intermediate 6f was synthesized in analogy to intermediate 6a, starting from trans 3-(4-chlorophenyl)-cyclobutan carboxylic acid (prepared as described in literature for the preparation of trans 3-phenyl-cyclobutan-carboxylic acid: Wiberg, K. B.; Dailey, W. P.; Walker, F. H.; Waddell, S. T.; Crocker, L. S.; Newton, M. Journal of the American Chemical Society; 1985, 107, 7247-7257).

Intermediate 6g



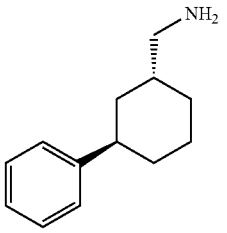
Intermediate 6g was synthesized in analogy to Intermediate 6a, starting from cis 3-(4-chlorophenyl)-cyclobutan carboxylic acid (prepared as described in literature for the preparation of cis 3-phenyl-cyclobutan-carboxylic acid: Wiberg, K. B.; Dailey, W. P.; Walker, F. H.; Waddell, S. T.; Crocker, L. S.; Newton, M. Journal of the American Chemical Society; 1985, 107, 7247-7257).

Intermediate 7a



Intermediate 4a (390 mg, 2.10 mmol) and Raney-Nickel (10 mg) in 10 ml of 1M solution of ammonia in ethanol was stirred under a hydrogen atmosphere (4 bar) overnight. The reaction mixture was filtered on a celite pad and concentrated under vacuum. The crude product was purified by flash chromatography (dichloromethane/methanol/NH_3 (30% aqueous solution)=95/5/0.1%) to obtain 217 mg (1.15 mmol) of the desired product.

Intermediate 7b



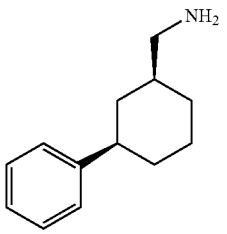
2.85 ml of a 1M solution of lithium aluminium hydride (2.85 mmol) in tetrahydrofuran was dissolved in 10 ml of tetrahydrofuran and stirred at 0° C. under nitrogen atmosphere.

Intermediate 6a (145 mg, 0.71 mmol) in 10 ml of tetrahydrofuran was added dropwise. The reaction mixture was stirred at 0° C. for 2 h and then quenched with water and ice. The reaction mixture was extracted with dichloromethane. The organic phase was washed with a 1M aqueous solution of sodium hydroxide, brine, dried over sodium sulfate and concentrated under vacuum. 100 mg (0.55 mmol) of the desired product were obtained.

GC/MS (method 3A) R_t=11.53 min

$[M]^+$=189

Intermediate 7c

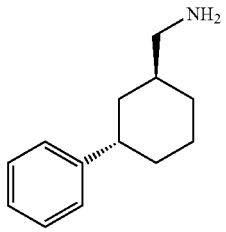


was synthesized in analogy to Intermediate 7b, starting from Intermediate 6b.

GC/MS (method 3A) R_t=11.47 min

$[M]^+$=189

Intermediate 7d

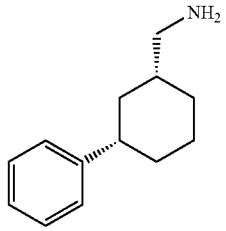


was synthesized in analogy to Intermediate 7b, starting from Intermediate 6c.

GC/MS (method 3A) R_t=11.53 min

$[M]^+$=189

Intermediate 7e

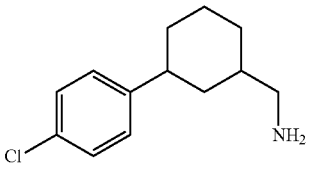
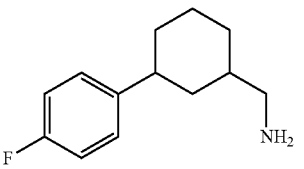
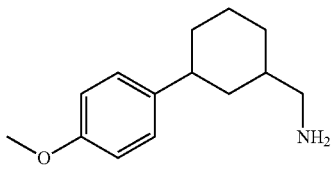


was synthesized in analogy to Intermediate 7b, starting from Intermediate 6d.

GC/MS (method 3A) R_t=13.03 min

$[M]^+$=189

The following intermediates were synthesised in atalogy to Intermediate 7a.

Starting Intermediate	Intermediate	STRUCTURE
4d	7f	
4e	7g	
4f	7h	

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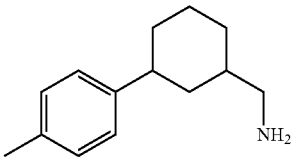
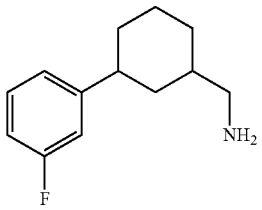
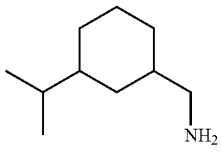
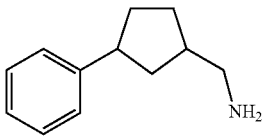
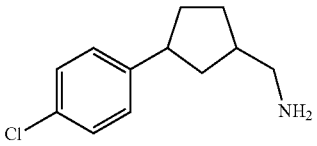
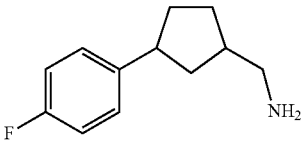
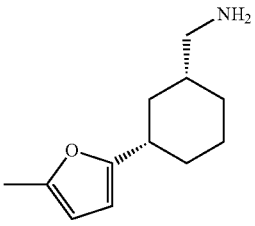
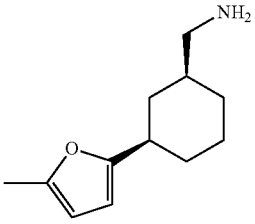
Starting Intermediate	Intermediate	STRUCTURE
4g	7i	
4h	7j	
4i	7k	
4k	7l	
4l	7m	
4m	7n	
4n	7o	
4o	7p	

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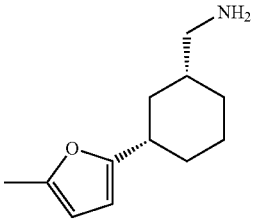
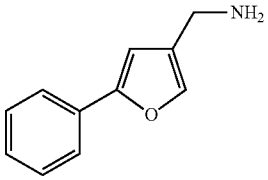
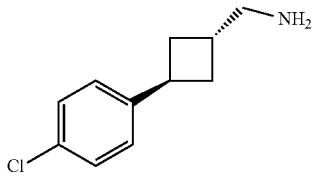
Starting Intermediate	Intermediate	STRUCTURE
4p	7q	

Intermediate 7r



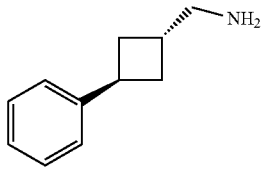
was synthesized in analogy to intermediate 7b, starting from intermediate 6e.

Intermediate 7s



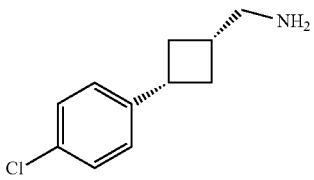
was synthesized in analogy to intermediate 7b, starting from intermediate 6f.

Intermediate 7t



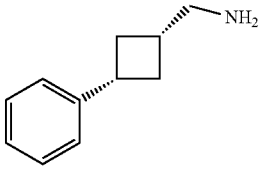
was obtained and isolated as side product in the preparation of Intermediate 7s

Intermediate 7u



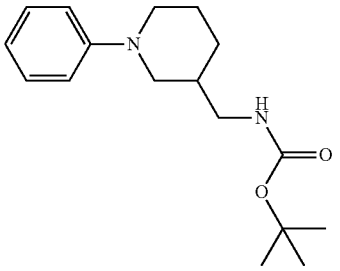
was synthesized in analogy to Intermediate 7b, starting from Intermediate 6g.

Intermediate 7v



was obtained and isolated as side product in the preparation of Intermediate 7u.

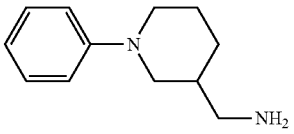
Intermediate 8a



Tris(dibenzylideneacetone)dipalladium (1.71 g, 1.87 mmol) and 2,2'-bis(diphenylphosphino)-1,1'-binapthyl (2.32 g, 3.72 mmol) were stirred in 30 ml of toluene for 10 min under argon atmosphere.

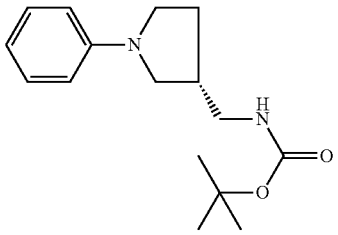
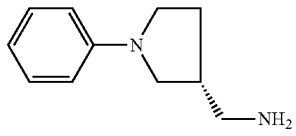
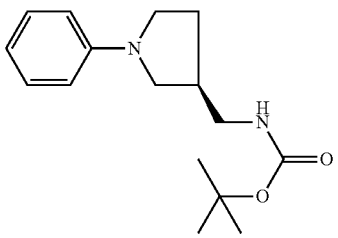
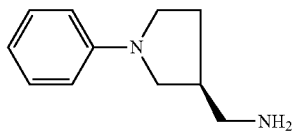
Piperidine-3-yl-methyl-carbamic acid tert-butyl ester (2 g, 9.33 mmol), bromobenzene (1.27 ml, 0.01 mol) and sodium tert-butoxide (1.43 g, 14.93 mmol) were added and the reaction mixture was stirred under reflux overnight. The reaction mixture was concentrated under vacuum, the crude product was dissolved in dichloromethane and the organic phase was filtered on a celite pad. The organic phase was washed with an aqueous saturated sodium carbonate solution, with brine, dried over sodium sulfate, concentrated under vacuum. The crude product obtained was dissolved in methanol and loaded onto a SCX cartridge (25 g). After washing with methanol the product was eluted with a 2M solution of ammonia in methanol. 1.17 g (4.03 mmol) of the desired product were obtained and used in next steps without any other purification.

Intermediate 9a



To a solution of Intermediate 8a (1.1 g, 3.79 mmol) in 10 ml of 1,4-dioxane, a 4M solution of hydrochloric acid in 1,4-dioxane (15 ml, 60 mmol) was added dropwise; the reaction mixture was stirred at room temperature overnight before being concentrated under vacuum. The crude product was purified by flash chromatography (Isolute silica gel cartridge: 50 g; eluent: dichloromethane/methanol=95/5%). 250 mg (1.31 mmol) of the desired compound were obtained.

The following intermediates were synthesized in analogy to Intermediates 8a and 9a.

Starting amine	Starting bromide	Intermediate	STRUCTURE	Intermediate	STRUCTURE
(S)-1-Pyrrolidin-3-ylmethyl-carbamic acid tert-butyl ester	bromo-benzene	8b		9b	 HCl
(R)-1-Pyrrolidin-3-ylmethyl-carbamic acid tert-butyl ester	bromo-benzene	8c		9c	 HCl

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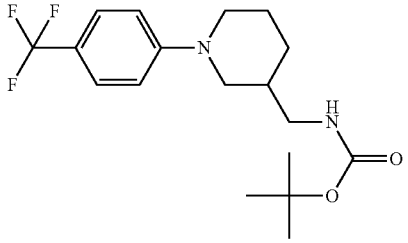
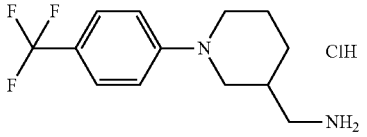
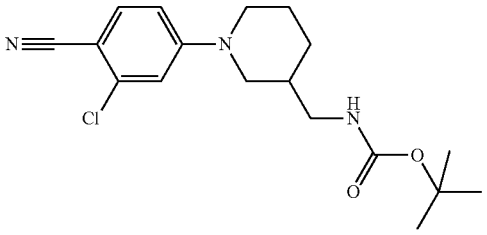
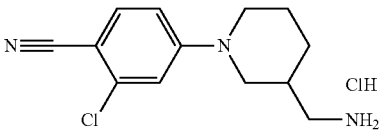
Starting amine	Starting bromide	Intermediate	STRUCTURE	Intermediate	STRUCTURE
Piperidine-3-yl-methyl-carbamic acid tert-butyl ester	1-bromo-4-trifluoro methyl-benzene	8d		9d	

Intermediate 10



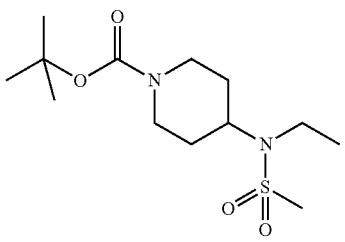
Piperidine-3-yl-methyl-carbamic acid tert-butyl ester (100 mg, 0.47 mmol), 2-chloro-4-fluoro-benzonitrile (72.5 mg, 0.47 mmol) and N,N-diisopropylethylamine (0.160 ml, 1.23 mmol) were dissolved in 10 ml of DMF and the reaction mixture was stirred at 125° C. overnight. The reaction mixture was concentrated under vacuum and the crude product was purified by flash chromatography (Isolute silica gel cartridge: 5 g; eluent: ethyl acetate). 125 mg (0.36 mmol) of the desired compound were obtained.

Intermediate 11



To a solution of Intermediate 10 (125 mg, 0.36 mmol) in 5 ml of 1,4-dioxane, a 4M solution of hydrochloric acid in 1,4-dioxane (0.12 ml, 480 mmol) was added dropwise; the reaction mixture was stirred at room temperature overnight before being concentrated under vacuum. 102 mg (0.36 mmol) of the desired compound were obtained.

Intermediate 12

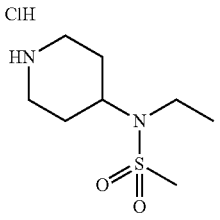


A solution of 4-methanesulfonylamino-piperidine-1-carboxylic acid tert-butyl ester (500 mg; 1.79 mmol) in 5 ml of acetonitrile was cooled to −5° C., iodoethane (308 mg, 1.79 mmol) and sodium hydride (96 mg, 3.59 mmol) were added; the reaction mixture was allowed to warm to room temperature and stirred for 72 h.

The reaction mixture was concentrated under vacuum; the residue was dissolved in ethyl acetate and washed with an aqueous saturated sodium bicarbonate solution and then with water.

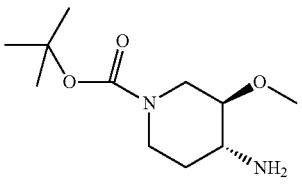
The organic phase was dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography (Isolute silica gel cartridge: 10 g, eluent: dichloromethane) to obtain 332 mg (1.1 mmol) of the desired compound.

Intermediate 13



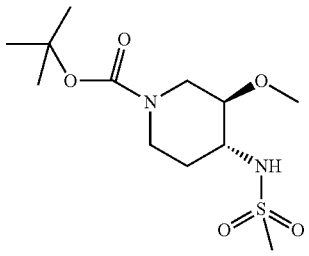
To a solution of intermediate 12 (330 mg, 1.1 mmol) in 20 ml of 1,4-dioxane, a 4M solution of hydrochloric acid in 1,4-dioxane (4.06 ml, 16 mmol) was added dropwise; the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum to obtain 262 mg (1.1 mmol) of the desired compound.

Intermediate 14



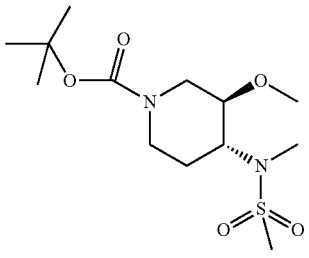
trans-4-Azido-3-methoxy-piperidine-1-carboxylic acid tert-butyl ester (1.6 g, 6.24 mmol), Pd/C 10% (200 mg) and acetic acid (1.6 ml) were dissolved in 25 ml of methanol and the reaction mixture was stirred under hydrogen atmosphere (4 bar) for 3 h. The reaction mixture was filtered on a celite pad and concentrated under vacuum. The crude product was purified by flash chromatography (Biotage SP1 cartridge 65i, eluent: dichloromethane/methanol=95/5%). 900 mg (3.91 mol) of the desired compound were obtained.

Intermediate 15a



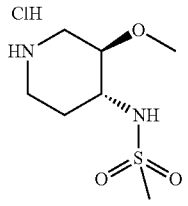
Intermediate 14 (900 mg, 3.91 mmol) and N,N-diisopropylethylamine (0.86 ml, 5 mmol were dissolved in 25 ml of dichloromethane. The reaction mixture was cooled to 0° C. and methanesulfonylchloride (0.33 ml, 4.30 mmol) was added. The reaction mixture was stirred at 0° C. for 20 min, then, water was added. The organic phase was separated, washed with an aqueous saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Isolute silica cartridge: 10 g, eluent: hexane/ethyl acetate=50/50%). 170 mg (0.55 mol) of the desired compound were obtained.

Intermediate 15b



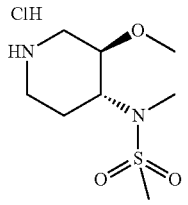
Intermediate 15a (350 mg, 1.13 mmol) and potassium carbonate (157 mg, 1.13 mmol) were dissolved and stirred in 15 ml of acetonitrile. A solution of iodomethane (0.071 ml, 1.13 mmol) in 5 ml of acetonitrile was added dropwise and the reaction mixture was warmed to 60° C. overnight. The reaction mixture was concentrated under vacuum and the crude product was dissolved in ethyl acetate. The organic phase was washed with an aqueous saturated sodium bicarbonate solution, separated, dried over sodium sulfate and concentrated under vacuum. 300 mg (0.93 mmol) of the desired compound were obtained and used in the next steps without further purification.

Intermediate 16a



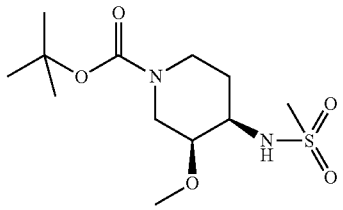
Intermediate 15a (170 mg, 0.55 mmol) in 2 ml of 1,4-dioxane was stirred at 10° C. A 4M solution of hydrochloric acid in 1,4-dioxane (8 ml, 32 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated under vacuum to obtain 115 mg (0.55 mmol) of the desired compound.

Intermediate 16b



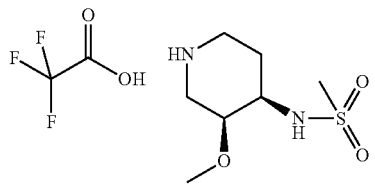
was synthesized in analogy to Intermediate 16a, starting from Intermediate 15b.

Intermediate 17



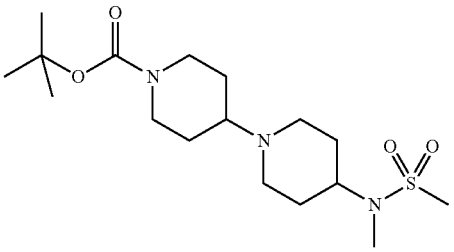
was synthesized in analogy to Intermediate 15a, starting from (3S,4R)-4-amino-3-methoxy-piperidine-1-carboxylic acid tert-butyl ester.

Intermediate 18



Intermediate 17 (660 mg, 2.14 mmol) in 10 ml of 1,4-dioxane was stirred at 10° C. Trifluoroacetic acid (2 ml, 26 mmol) was added dropwise and the reaction mixture was stirred at room temperature 18 h. The reaction mixture was concentrated under vacuum to obtain 600 mg (1.86 mmol) of the desired compound, used in the next step without further purification.

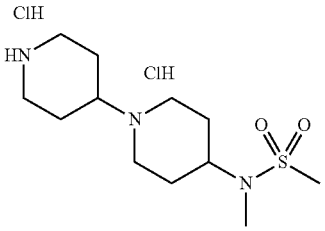
Intermediate 19a



N-methyl-N-piperidin-4-yl-methanesulfonamide hydrochloride (11 g, 47.91 mmol) was suspended in 200 ml of 1,2-dichloroethane, N,N-diisopropylethylamine (17.12 ml, 96.17 mmol) and 1-(tert-butoxycarbonyl)-piperidin-4-one (9.58 g, 48.08 mmol) were added and the reaction mixture was stirred at room temperature for 30 min Sodium triacetoxyborohydride (12.23 g, 57.50 mmol) was added and the reaction mixture was stirred at room temperature for 72 h. The reaction mixture was diluted with dichloromethane and washed with an aqueous saturated sodium bicarbonate solution.

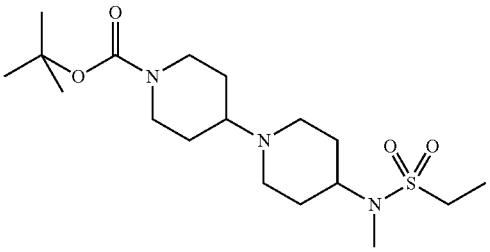
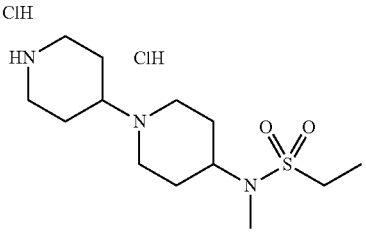
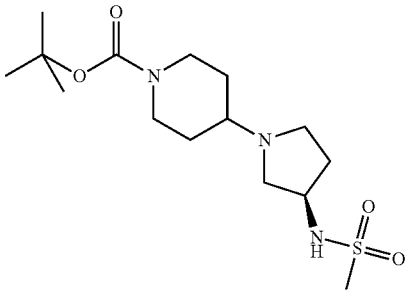
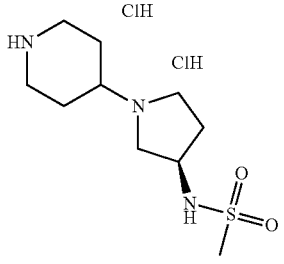
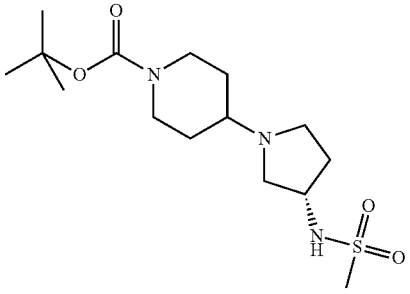
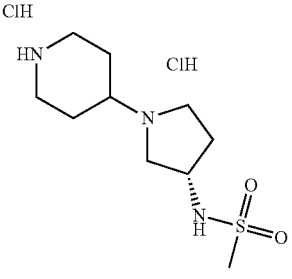
The organic phase was dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Biotage SP1; silica gel cartridge: 65i; eluent: ethyl acetate/methanol=50/50%) to obtain 7.2 g (19.2 mmol) of the desired compound.

Intermediate 20a



Intermediate 19a (7.2 g, 19.2 mmol) was suspended in 20 ml of 1,4-dioxane, a 4M solution of hydrochloric acid (48 ml, 192 mmol) in 1,4-dioxane was added dropwise. The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum. 6.3 g (18 mmol) of the desired compound were obtained.

The following intermediates were synthesized in analogy to Intermediates 19a and 20a.

Starting ketone	Starting amine	Carbamate Intermediate	STRUCTURE	Diamino Intermediate	STRUCTURE
1-(tert-butoxycarbonyl)-4-oxopiperidine	Ethanesulfonic acid methyl-piperidin-4-yl-amide	19b		20b	
1-(tert-butoxycarbonyl)-4-oxopiperidine	(R)-N-Pyrrolidin-3-yl-methane sulfonamide	19c		20c	
1-(tert-butoxycarbonyl)-4-oxopiperidine	(S)-N-Pyrrolidin-3-yl-methane sulfonamide	19d		20d	

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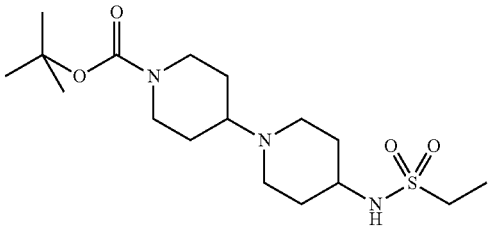
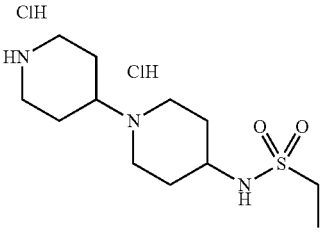
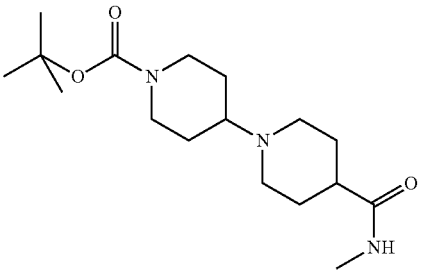
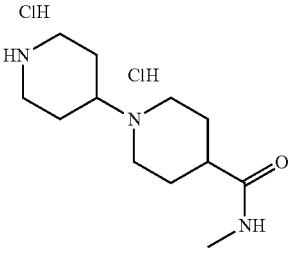
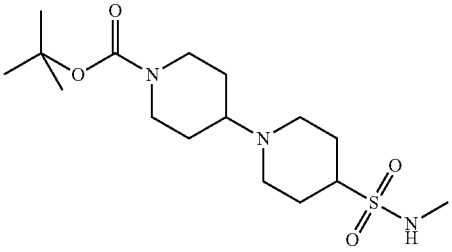
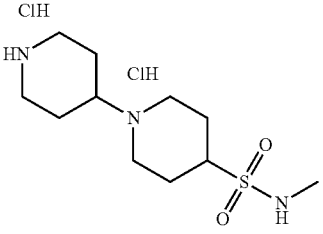
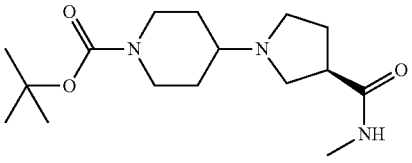
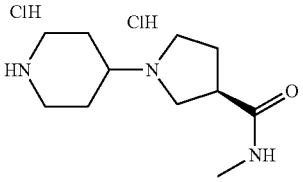
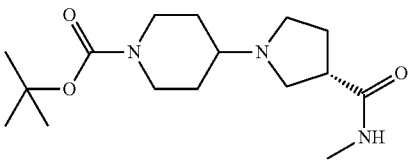
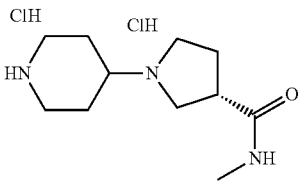
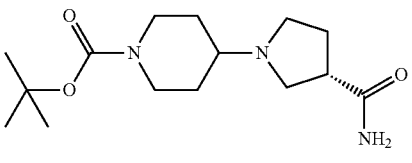
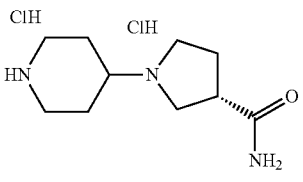
Starting ketone	Starting amine	Carbamate Intermediate	STRUCTURE	Diamino Intermediate	STRUCTURE
1-(tert-butoxycarbonyl)-4-oxopiperidine	Ethanesulfonic acid piperidin-4-ylamide	19e		20e	
1-(tert-butoxycarbonyl)-4-oxopiperidine	Piperidine-4-carboxylic acid methyl amide	19f		20f	
1-(tert-butoxycarbonyl)-4-oxopiperidine	Piperidine-4-sulfonic acid methyl amide	19g		20g	
1-(tert-butoxycarbonyl)-4-oxopiperidine	(R)-Pyrrolidine-3-carboxilic acid methylamide	19h		20h	
1-(tert-butoxycarbonyl)-4-oxopiperidine	(S)-Pyrrolidine-3-carboxilic acid methylamide	19i		20i	
1-(tert-butoxycarbonyl)-4-oxopiperidine	(S)-Pyrrolidine-3-carboxilic acid amide	19j		20j	

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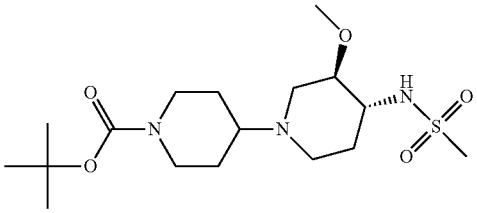
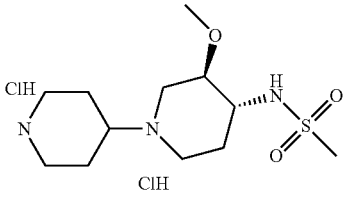
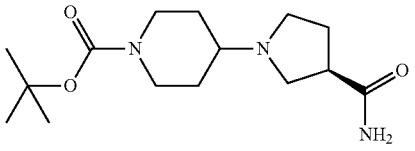
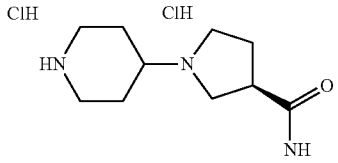
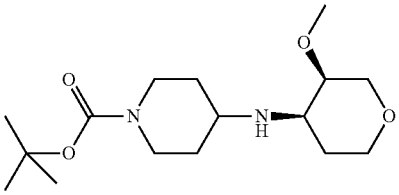
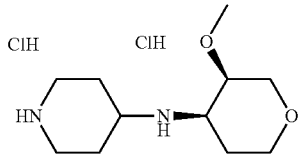
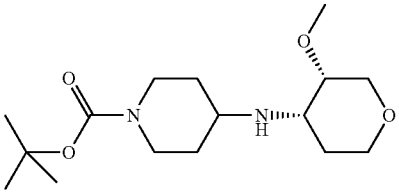
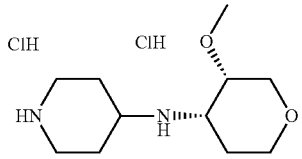
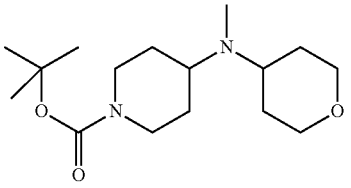
Starting ketone	Starting amine	Carbamate Intermediate	STRUCTURE	Diamino Intermediate	STRUCTURE
1-(tert-butoxycarbonyl)-4-oxo-piperidine	16a	19k		20k	
1-(tert-butoxycarbonyl)-4-oxo-piperidine	(R)-Pyrrolidine-3-carboxilic acid amide	19l		20l	
1-(tert-butoxycarbonyl)-4-oxo-piperidine	47b	19lf		20lf	
1-(tert-butoxycarbonyl)-4-oxo-piperidine	47c	19lg		20lg	

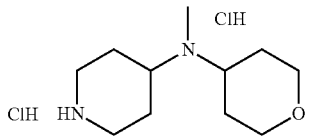
Intermediate 19la



4-Methylamino-piperidine-1-carboxylic acid tert-butyl ester (500 mg, 1.87 mmol) was suspended in 10 ml of 1,2-dichloroethane. Tetrahydro-pyran-4-one (0.17 ml, 1.87 mmol) was added and the reaction mixture was stirred at room temperature for 30 min Sodium triacetoxyborohydride (593 mg, 2.80 mol) was added and the reaction mixture was stirred for 18 h. The reaction mixture was diluted with dichloromethane and washed with an aqueous saturated sodium bicarbonate solution.

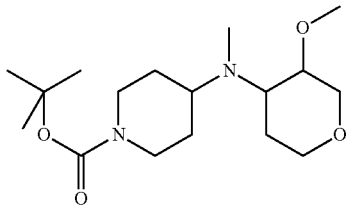
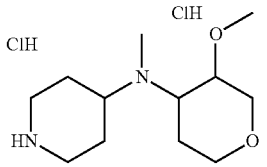
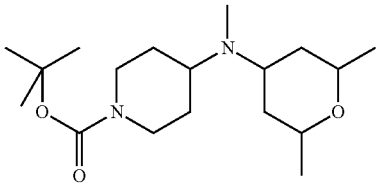
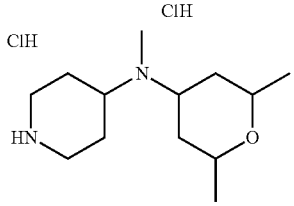
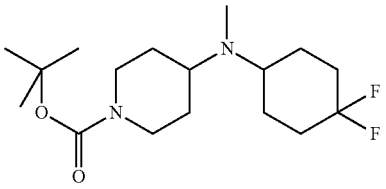
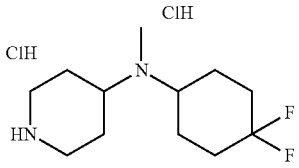
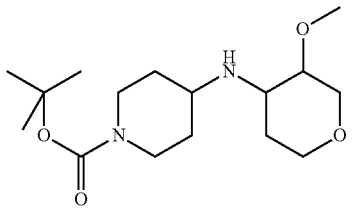
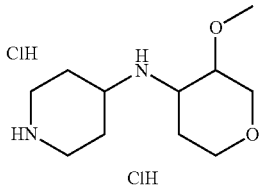
The organic phase was dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Isolute silica gel cartridge 10 g; eluent: dichloromethane/methanol=94/6%). 240 mg (0.80 mmol) of the desired compound were obtained.

Intermediate 20la

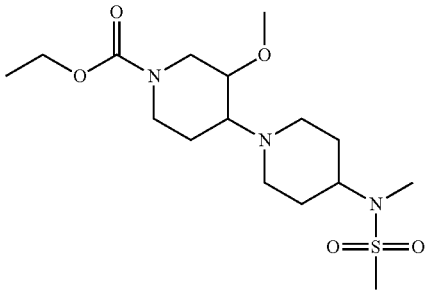


Intermediate 191a (240 mg, 0.80 mmol) was suspended in 10 ml of 1,4-dioxane, a 4M solution of hydrochloric acid (2.0 ml, 8.0 mmol) in 1,4-dioxane was added dropwise. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated under vacuum. 200 mg (0.74 mmol) of the desired compound were obtained.

The following intermediates were synthesized in analogy to Intermediates 191a and 201a

Starting amine	Starting ketone	Carbamate Intermediate	STRUCTURE	Amino Intermediate	STRUCTURE
4-Methylamino-piperidine-1-carboxylic acid tert-butyl ester	3-Methoxy-tetrahydropyran-4-one	19lb		20lb	
4-Methylamino-piperidine-1-carboxylic acid tert-butyl ester	2,6-dimethyltetrahydropyran-4-one	19lc		20lc	
4-Methylamino-piperidine-1-carboxylic acid tert-butyl ester	4,4-difluorocyclohexanone	19ld		20ld	
4-amino-piperidine-1-carboxylic acid tert-butyl ester	3-Methoxy-tetrahydropyran-4-one	19le		20le	

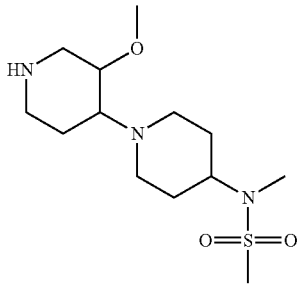
Intermediate 19m



N-methyl-N-piperidin-4-yl-methanesulfonamide hydrochloride (1.13 g, 4.95 mmol) was suspended in 10 ml of 1,2-dichloroethane, N,N-diisopropylethylamine (2.6 ml, 14.9 mmol) and N-carbethoxy-3-methoxy-piperidin-4-one (1 g, 4.95 mmol) were added and the reaction mixture was stirred at room temperature for 30 min Sodium triacetoxyborohydride (3.16 g, 14.85 mol) was added and the reaction mixture was stirred at room temperature for 72 h. The reaction mixture was diluted with dichloromethane and washed with an aqueous saturated sodium bicarbonate solution.

The organic phase was dried over sodium sulfate and concentrated under vacuum. 1.5 g (3.97 mmol) of the desired compound were obtained and used without further purification.

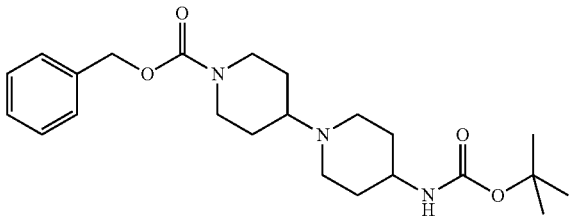
Intermediate 20m



Intermediate 19m (1.5 g, 3.97 mmol) and potassion hydroxide (4.46 g, 7.94 mmol) were suspended in 25 ml of ethanol and the reaction mixture was stirred under reflux overnight.

The reaction mixture was concentrated under vacuum and the crude product was loaded on a SCX cartridge (25 g) and eluted with a 2M solution of ammonia in methanol. 1.2 g (3.97 mmol) of the desired compound were obtained.

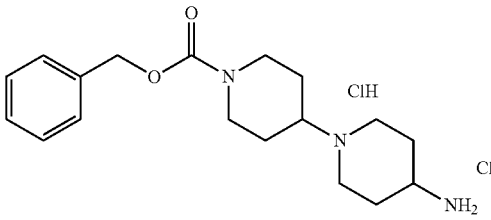
Intermediate 21



Piperidin-4-yl-carbamic acid tert-butyl ester (6 g, 30 mmol) and 1-(benzyloxycarbonyl)-4-oxopiperidine (9.6 g, 48 mmol) were dissolved in 50 ml of dichloromethane and the reaction mixture was stirred at room temperature for 30 min; sodium triacetoxyborohydride (12.23 g, 57.5 mmol) was added and the reaction mixture was stirred at room temperature overnight.

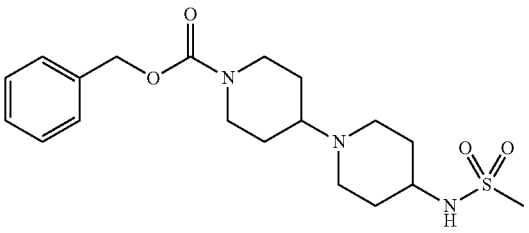
The reaction mixture was diluted with dichloromethane and washed with an aqueous saturated sodium bicarbonate solution. The organic phase was dried over sodium sulfate and concentrated under vacuum. The crude product was treated with acetone/isopropyl ether and the precipitate obtained was filtered off. 8.4 g (20 mmol) of the desired product were obtained.

Intermediate 22



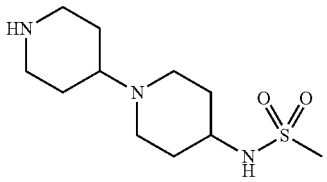
To a solution of intermediate 21 (8.4 g, 20 mmol) in 150 ml of 1,4-dioxane previously cooled to 0° C., 12.6 ml (50 mmol) of a 4M solution of hydrochloric acid in 1,4-dioxane were added dropwise; the reaction mixture was allowed to warm to room temperature and was stirred at that temperature overnight. The solid precipitated from the reaction mixture was filtered off and dried at 50° C. under vacuum to obtain 6 g (15 mmol) of the desired compound.

Intermediate 23



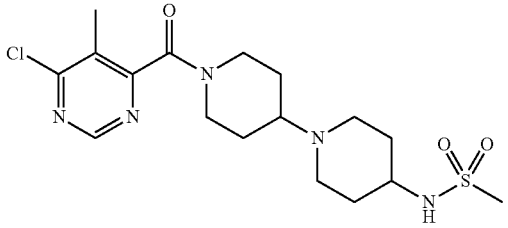
Intermediate 22 (6.0 g, 15 mmol) was suspended in 55 ml of dichloromethane; triethylamine (6.43 ml, 46 mmol) was added and the reaction mixture was cooled to 0° C. and stirred at that temperature for 30 min Methanesulfonyl chloride (1.43 ml, 18 mmol) in 5 ml of dichloromethane was added dropwise. The reaction mixture was stirred at 0° C. for 1 h; then water was added and the reaction mixture was extracted with dichloromethane. The organic phase was washed with an aqueous saturated sodium bicarbonate solution, with brine, dried over sodium sulfate and concentrated under vacuum. The crude product was treated with diisopropyl ether, the precipitate was filtered off and dried. 5 g (13 mmol) of the desired product were obtained.

Intermediate 24



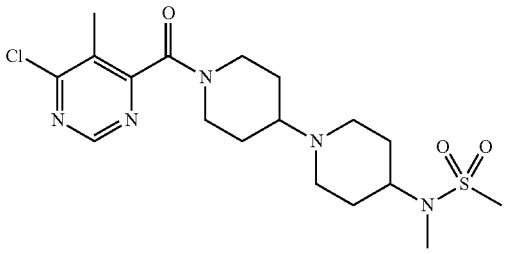
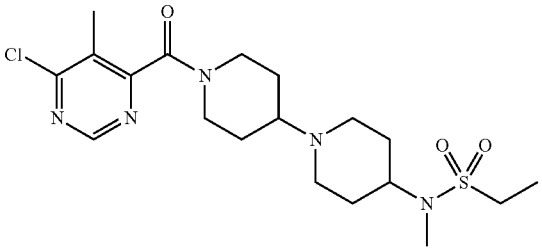
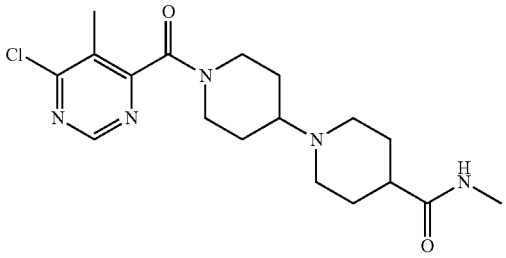
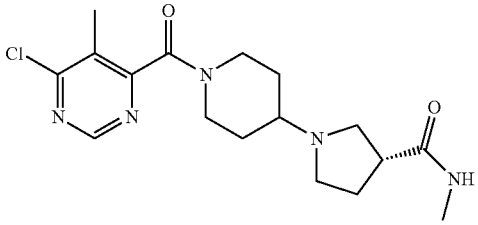
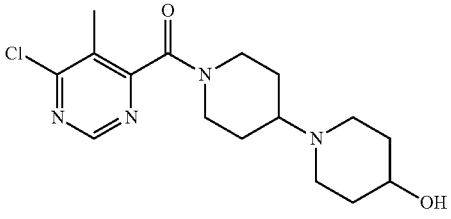
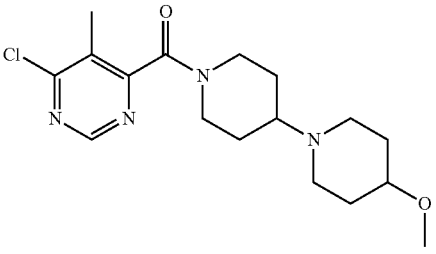
Intermediate 23 (5 g, 13 mmol) was dissolved in 50 ml of methanol; acetic acid (1.5 ml, 25.3 mmol) and Pd/C 10% (500 mg) were added in sequence and the reaction mixture was stirred under a hydrogen atmosphere (3 bar) at room temperature for 5 days. The reaction mixture was filtered on a celite pad and the organic phase was loaded on a SCX cartridge (10 g). After washing with methanol, the desired compound was eluted with a 2M solution of ammonia in methanol. 3.7 g (4.6 mmol) of the title compound were obtained.

Intermediate 25a



Intermediate 24 (1.1 g, 4.21 mmol) was suspended in 20 ml of dry dichloromethane, N,N-diisopropylethylamine (1.47 ml, 8.42 mmol) and DMF (137 µl, 1.67 mmol) were added and the reaction mixture was stirred under nitrogen atmosphere and cooled to 0° C. Intermediate 2a (812 mg, 4.21 mmol) in 5 ml of dichloromethane was added dropwise and the reaction mixture was allowed to warm up to room temperature and stirred for 1.5 h; the reaction mixture was diluted with dichloromethane and washed with an aqueous saturated sodium bicarbonate solution. The organic phase was separated, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (isolute silica gel cartridge: 10 g; eluent: dichloromethane/methanol=95/5%). 1.0 g (2.41 mmol) of the title compound were obtained.

The following intermediates were synthesized in analogy to Intermediate 25a.

Core Intermediate	Piperidine Intermediate	Chloropyrimidine Intermediate	STRUCTURE
2a	20a	25b	
2a	20b	25c	
2a	20f	25d	
2a	20h	25e	
2a	[1,4']-Bipiperidinyl-4-ol	25f	
2a	4-Methoxy-[1,4']bipiperidinyl	25g	

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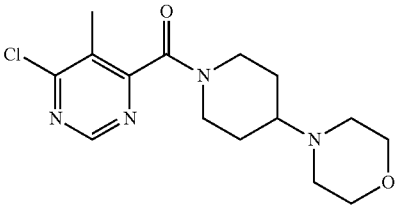
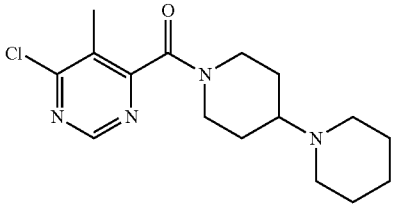
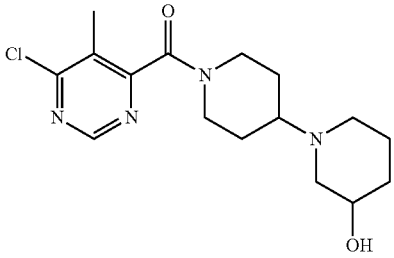
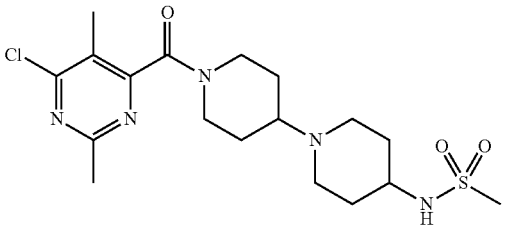
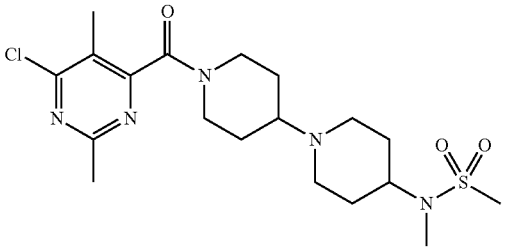
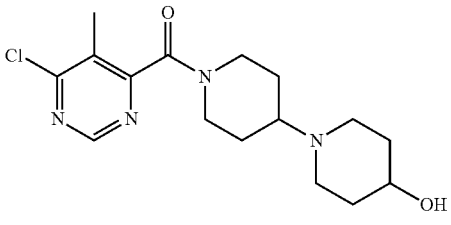
Core Inter-mediate	Piperidine Inter-mediate	Chloro-pyrimidine Intermediate	STRUCTURE
2a	4-Piperidin-4-yl-morpholine	25h	
2a	[1,4']Bi-piperidinyl	25i	
2a	[1,4']-Bi-piperidinyl-3-ol	25j	
2b	24	25k	
2b	20a	251	
2b	[1,4']-Bi-piperidinyl-4-ol	25m	

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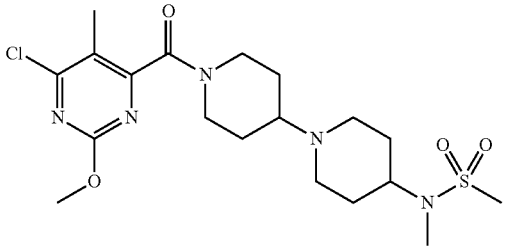
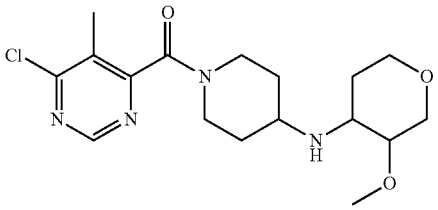
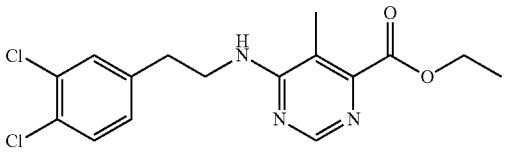
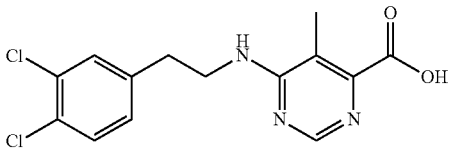
Core Intermediate	Piperidine Intermediate	Chloro-pyrimidine Intermediate	STRUCTURE
2c	20a	25n	
2a	20le	25o	

Intermediate 26a



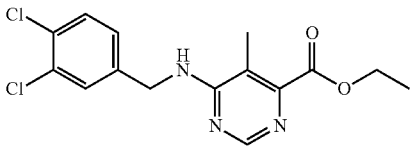
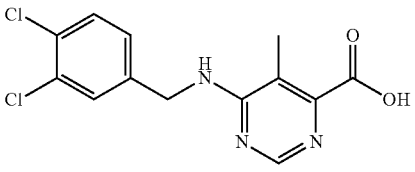
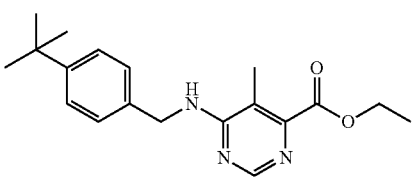
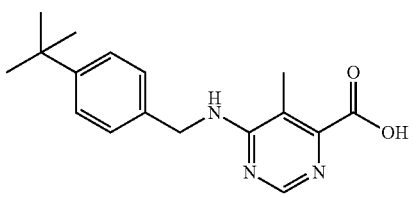
Intermediate 27a



Intermediate 3a (10 g, 49.35 mmol) and N,N-diisopropyl-ethylamine (17 ml, 99 mmol) were dissolved in 20 ml of dry DMF; 2-(3,4-dichloro-phenyl)-ethylamine (9.57 g, 49.35 mmol) in 10 ml of dry DMF was added and the reaction mixture was stirred at 90° C. for 2 h. The reaction mixture was cooled to room temperature, water was added and the reaction mixture was extracted with dichloromethane; the organic phase was concentrated under vacuum, the crude product was suspended and stirred in diethyl ether and the precipitate was filtered off and dried. 10.2 g (28.8 mmol) of the desired compound were obtained.

Intermediate 26a (10.0 g, 28.25 mmol) was dissolved in 70 ml of ethanol and a solution of LiOH (3.52 g, 83.88 mmol) in 70 ml of water was added. The reaction mixture was stirred at 70° C. for 1 hour, concentrated under vacuum and the remaining aqueous solution was acidified by 20 ml of 4M solution of hydrochloric acid in 1,4-dioxane; the precipitate formed was filtered off and dried. 8.6 g (26.37 mmol) of the desired product were obtained.

The following intermediates were synthesized in analogy to Intermediates 26a and 27a.

Core Intermediate	Amine	Ester Intermediate	STRUCTURE	Acid Intermediate	STRUCTURE
3a	3,4-Dichloro-benzyl-amine	26b		27b	
3b	4-tert-butyl-benzyl-amine	26c		27c	

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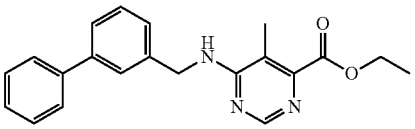
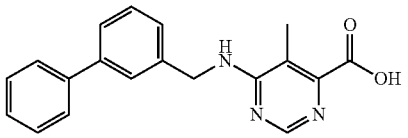
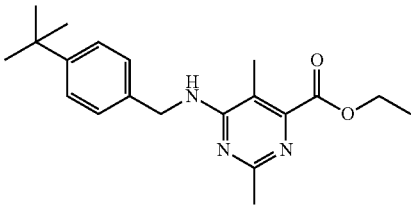
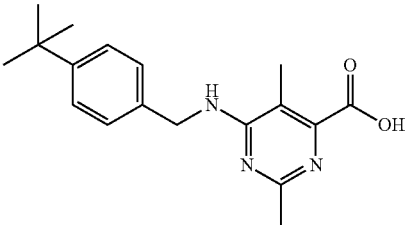
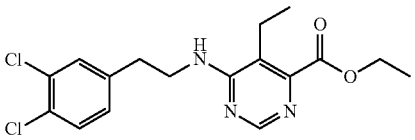
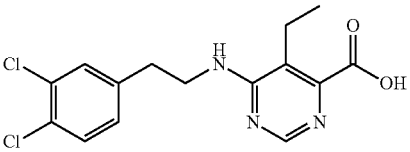
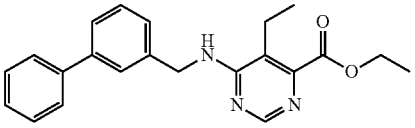
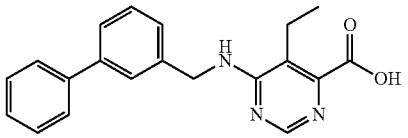
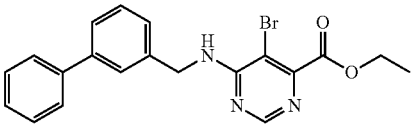
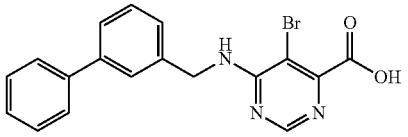
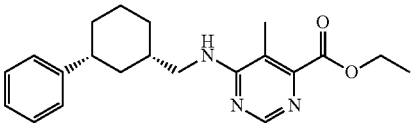
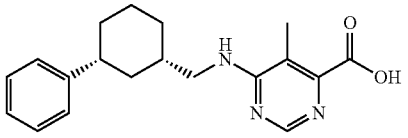
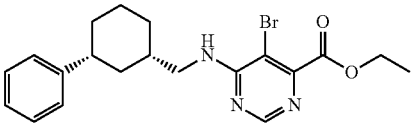
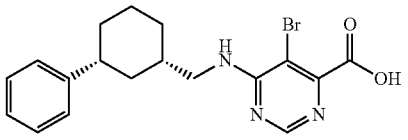
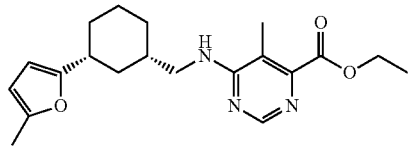
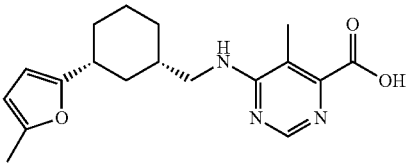
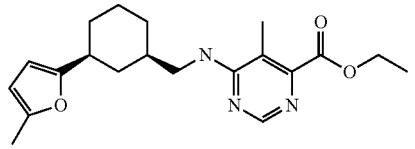
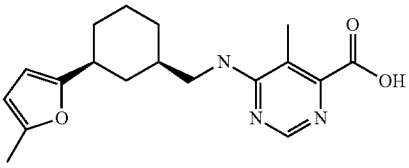
Core Intermediate	Amine	Ester Intermediate	STRUCTURE	Acid Intermediate	STRUCTURE
3a	biphenyl-3-ylmethanamine	26d		27d	
3b	4-tert-butylbenzylamine	26e		27e	
3c	2-(3,4-dichlorophenyl)ethylamine	26f		27f	
3c	biphenyl-3-yl-methanamine	26g		27g	
3d	biphenyl-3-yl-methanamine	26h		27h	
3a	Intermediate 7c	26ha		27ha	
3d	Intermediate 7c	26hb		27hb	
3a	Intermediate 7p	26hc		27hc	
3a	Intermediate 7q	26hd		27hd	

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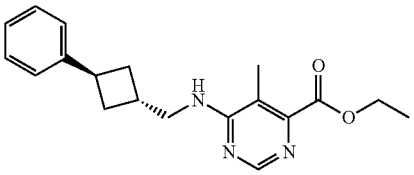
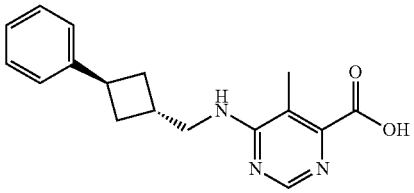
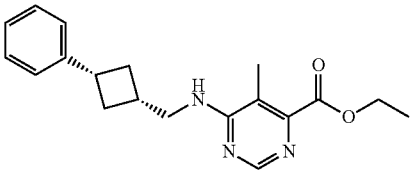
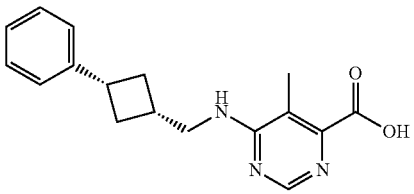
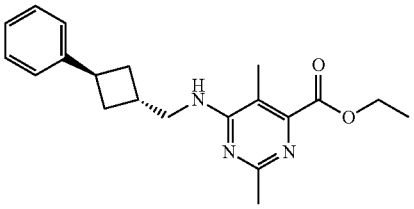
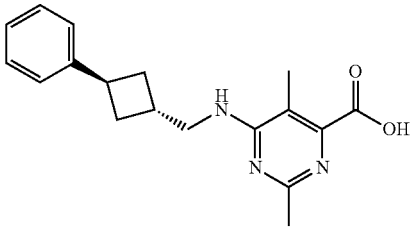
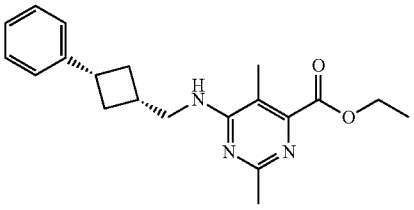
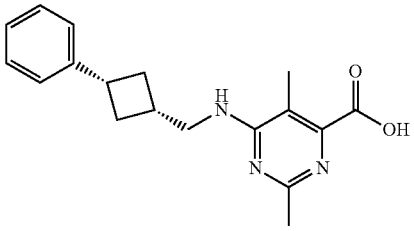
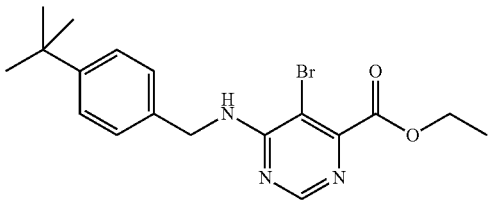
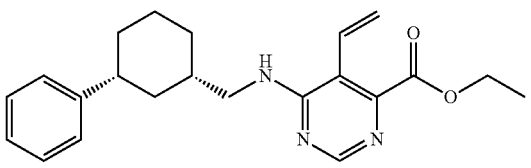
Core Intermediate	Amine	Ester Intermediate	STRUCTURE	Acid Intermediate	STRUCTURE
3a	Intermediate 7t	26he		27he	
3a	Intermediate 7v	26hf		27hf	
3b	Intermediate 7t	26hr		27hr	
3b	Intermediate 7v	26hs		27hs	

Intermediate 26i



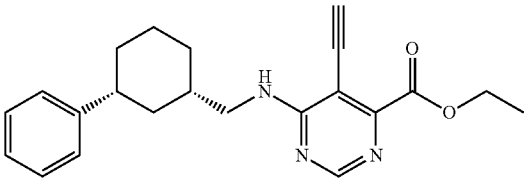
Intermediate 3d (2 g, 7.53 mmol) and N,N-diisopropylethylamine (1.97 ml, 11.3 mmol) were dissolved in 15 ml of dry DMF; 4-tertbutyl-benzylamine (1.6 ml, 9.04 mmol) was added and the reaction mixture was stirred at 60° C. for 18 h. The reaction mixture was cooled to room temperature, water was added and the reaction mixture was extracted with dichloromethane; the organic phase was concentrated under vacuum and the crude product was purified by flash chromatography (BIOTAGE SP1; silica gel cartridge: 65i; eluent: hexane/ethyl acetate=70/30%). 1.5 g (3.82 mmol) of the desired compound were obtained.

Intermediate 26ib



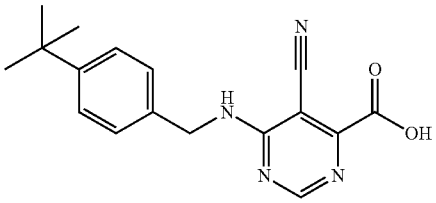
Intermediate 26hb (75 mg, 179 μmol), tributyl(vinyl)tin (200 μl, 685 μmol) and bis(triphenylphosphine)palladium chloride (13 mg, 18 μmol) were added to 3 ml 1,2-dichloroethane. The reaction mixture was heated in the microwave for 4 h at 120° C. Then, the solvent was removed in vacuum and the residue was purified by reversed phase HPLC to give the desired product (56 mg, 117 mmol).

Intermediate 26ic



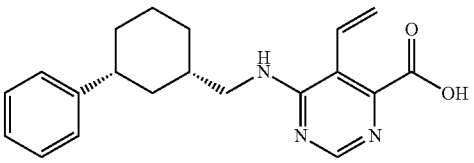
was synthesized in analogy to intermediate 26ib, starting from intermediate 26hb and tributyl(ethynyl)tin.

Intermediate 27i



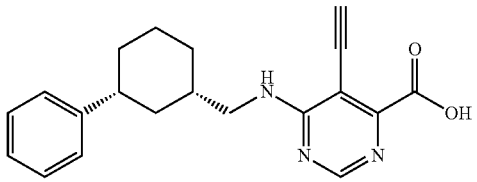
Intermediate 26i (500 mg, 1.27 mmol) and CuCN (114 mg, 1.27 mmol) were dissolved in 5 ml of DMA and the reaction mixture was stirred at 100° C. overnight. The reaction mixture was cooled, diluted with dichloromethane and the organic phase was washed with water, dried over sodium sulfate and concentrated under vacuum. 30 mg (0.1 mmol) of the crude product were obtained and used in the next step without purification.

Intermediate 27ib



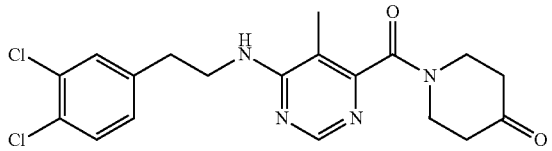
was synthesized in analogy to 27a starting from intermediate 26ib.

Intermediate 27ic



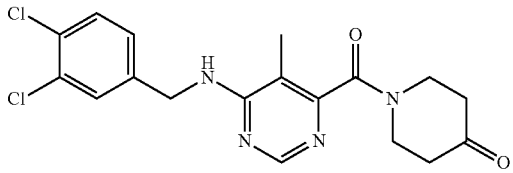
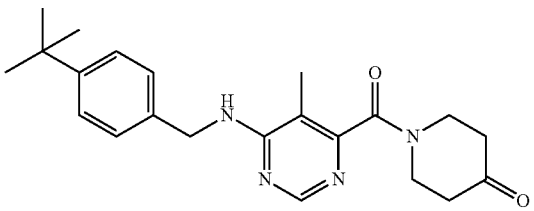
was synthesized in analogy to 27a starting from intermediate 26ic.

Intermediate 28a



Intermediate 27a (4 g, 12.14 mmol), TBTU (3.9 g, 12.14 mmol) and N,N-diisopropylethylamine (5.34 ml, 30.35 mmol) were dissolved in 25 ml of DMF. The reaction mixture was stirred under nitrogen atmosphere at room temperature for 30 min; then piperidin-4-one hydrochloride (1.66 g, 12.14 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum and the crude product was dissolved in dichloromethane. The organic phase was washed with a saturated aqueous solution of sodium bicarbonate, with a 1M aqueous solution of sodium hydroxide, with brine, then dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography (BIOTAGE SP1; silica gel cartridge: 65i; eluent: dichloromethane/methanol=95/5%). 2.2 g (5.4 mmol) of the desired compound were obtained.

The following intermediates were synthesized in analogy to intermediate 28a.

Acid Intermediate	Amine	Intermediate	STRUCTURE
27b	Piperidin-4-one	28b	
27c	Piperidin-4-one	28c	

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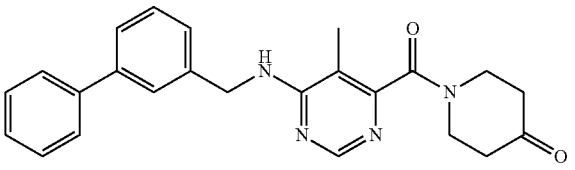
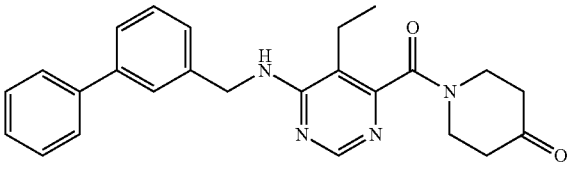
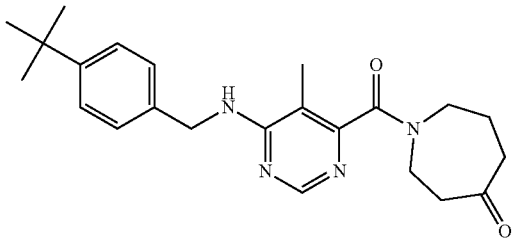
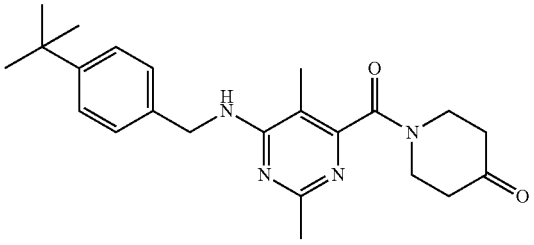
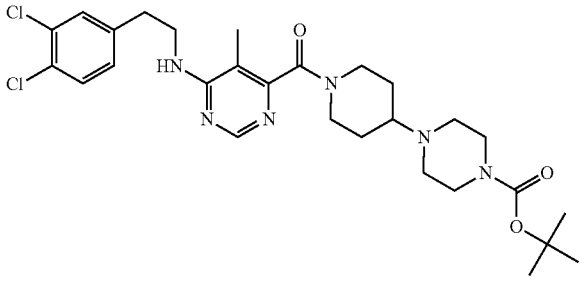
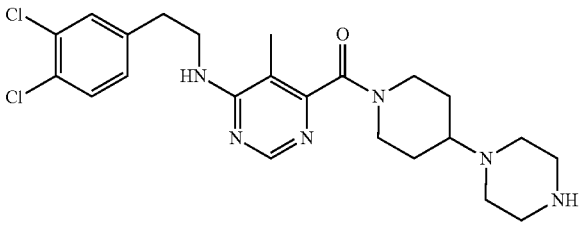
Acid Intermediate	Amine	Intermediate	STRUCTURE
27d	Piperidin-4-one	28d	
27g	Piperidin-4-one	28e	
27c	Azepan-4-one	28f	
27e	Piperidin-4-one	28g	

Intermediate 29



Intermediate 28a (500 mg, 1.22 mmol), piperazine-1-carboxylic acid tert-butyl ester (228 mg, 1.23 mmol) and 2-picoline borane complex (131.3 mg, 1.22 mmol) in 15 ml of methanol were stirred at room temperature for 72 h; the reaction mixture was concentrated under vacuum and the crude product was dissolved in dichloromethane. The organic phase was washed with water, dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography (Isolute silica gel cartridge: 20 g; eluent: dichloromethane/methanol=98/2%). 280 mg (0.48 mmol) of the desired compound were obtained.

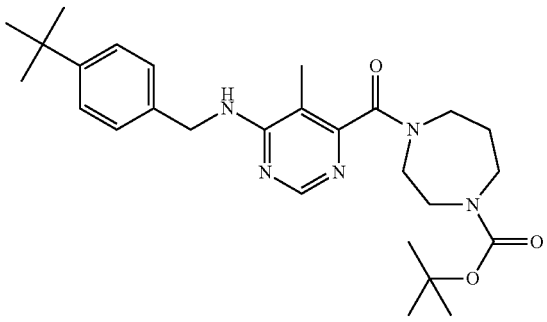
Intermediate 30



Intermediate 29 (280 mg, 0.48 mmol) was dissolved in 6 ml of 1,4-dioxane; 4 ml (16 mmol

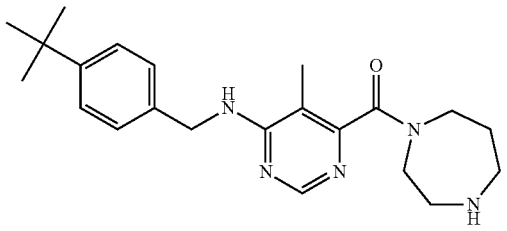
of a 4M solution of hydrochloric acid in 1,4-dioxane were added dropwise and the reaction mixture was stirred at room temperature overnight. The solvent was concentrated under vacuum. 240 mg (0.46 mmol) of the desired compound were obtained.

Intermediate 31



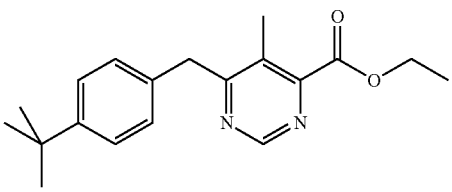
Intermediate 27c (500 mg, 1.67 mmol), TBTU (643 mg, 2 mmol) and N,N-diisopropylethylamine (0.29 ml, 1.67 mmol) were dissolved in 5 ml of DMF. The reaction mixture was stirred under nitrogen atmosphere at room temperature for 10 min; then [1,4]diazepan-1-carboxylic acid tert-butyl ester (334 mg, 1.67 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and washed with an aqueous saturated solution of sodium bicarbonate. The organic phase was separated, dried over sodium sulfate and concentrated under vacuum. The crude product was suspended in diisopropyl ether and stirred, the solid obtained was filtered and dried. 700 mg (1.45 mmol) of the desired compound were obtained.

Intermediate 32



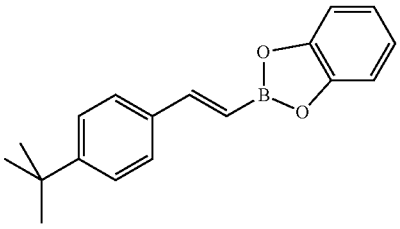
Intermediate 31 (600 mg; 1.24 mmol) was suspended in 5 ml of diethyl ether, 5 ml of a 1M solution of hydrochloric acid in diethyl ether was added dropwise and the reaction mixture was stirred at room temperature overnight. The solvent was concentrated under vacuum and the crude product was loaded on a SCX cartridge (10 g) and eluted with a 2M solution of ammonia in methanol. 470 mg (1.23 mmol) of the title compound were obtained.

Intermediate 33



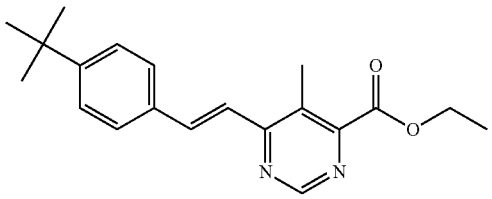
Intermediate 3a (1.5 g, 7.47 mmol) and tetrakis(triphenylphosphine)palladium (143.9 mg, 0.12 mmol) were suspended in 40 ml of toluene under nitrogen atmosphere; 4-tert-butyl-benzylzinc bromide (29.9 ml, 15 mmol) was added dropwise and then the reaction mixture was stirred at 20° C. for 8 h. 5 ml of methanol, 40 ml of water and 100 ml of dichloromethane were added. The organic phase was separated, dried over sodium sulfate and concentrated under vacuum. The crude product obtained was purified by flash chromatography (Biotage column 40M+; eluent: dichloromethane/ethyl acetate=95/5%). 230 mg (0.74 mmol) of the desired compound were obtained.

Intermediate 34



To a solution of 4-tert-butylphenylacetylene (5 ml, 28 mmol) in 20 ml of dry tetrahydrofuran under nitrogen atmosphere, a solution of catecholborane (3.41 ml, 31 mmol) in 20 ml of dry tetrahydrofuran was added dropwise. The reaction mixture was refluxed for 2 h and then concentrated under vacuum; the crude product obtained was dissolved in ethyl acetate and the organic phase was washed with a 2 M aqueous solution of hydrochloric acid. The organic phase was separated, washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude product obtained was purified by flash chromatography (Biotage column 40M+; eluent: dichloromethane/ethyl acetate=95/5%). 230 mg (0.82 mmol) of the desired compound were obtained.

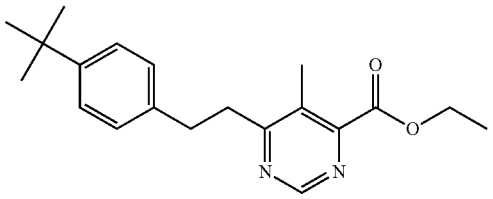
Intermediate 35



Intermediate 3a (600 mg, 3 mmol), intermediate 34 and tetrakis(triphenylphosphine)palladium (347 mg, 0.3 mmol) were dissolved in 3.6 ml of a 2 M aqueous solution of sodium carbonate and 40 ml of 1,2 dimethoxyethane. The reaction mixture was stirred at 80° C. overnight. Water was added and the reaction mixture was extracted with dichloromethane. The organic phase was separated, dried over sodium sulfate and concentrated under vacuum. The crude product obtained was purified by flash chromatography (Biotage column

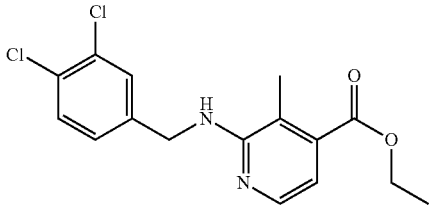
40M+; eluent: dichloromethane/ethyl acetate=95/5%). 550 mg (1.60 mmol) of the desired compound were obtained.

Intermediate 36



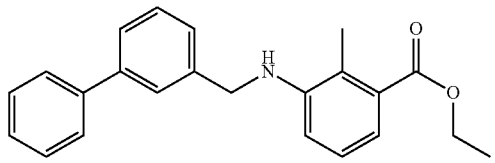
Intermediate 35 (250 mg, 0.77 mmol) was dissolved in 5 ml of ethanol and 5 ml of tetrahydrofuran. Pd/C (35 mg) was added and the reaction mixture was stirred under hydrogen atmosphere (1 atm) at room temperature overnight. The reaction mixture was filtered on a celite pad and concentrated under vacuum. 170 mg (0.52 mmol) of the desired compound were obtained.

Intermediate 37



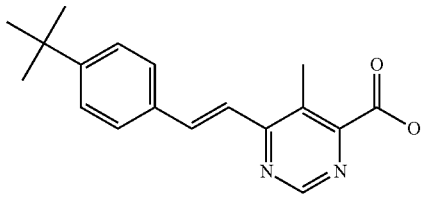
Palladium acetate (170 mg, 0.75 mmol) and 2,2'-bis(diphenylphosphino)-1,1'-binapthyl (936 mg, 1.5 mmol) were dissolved in 25 ml of 1,4-dioxane and stirred at 40° C. for 30 minutes. 2-chloro-3-methylpyridine-4-carboxylic acid ethyl ester (500 mg, 2.5 mmol), 3,4-dichlorobenzylamine (680 mg, 5 mmol) and cesium carbonate (715.5 mg, 3.76 mmol) were added and the reaction mixture was refluxed for 48 h. The solvent was concentrated under vacuum and the crude product was loaded on a SCX cartridge (10 g) and eluted with a 2M solution of ammonia in methanol. The solvent was concentrated under vacuum and the crude product obtained was purified by flash chromatography (Biotage column 25M+; eluent: ethyl acetate). 250 mg (0.73 mmol) of the desired compound were obtained.

Intermediate 38



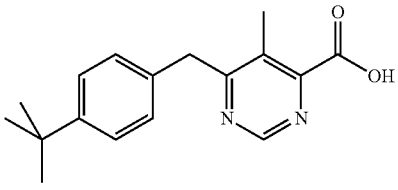
3-(Bromomethyl)biphenyl (150 mg, 0.58 mmol), sodium carbonate (188 mg, 1.75 mmol) and 3-amino-2-methyl-benzoic acid ethyl ester (0.1 ml, 0.58 mmol) were mixed in 2 ml of DMF and stirred at 100° C. for 2 hours. The solvent was then concentrated under vacuum and the crude product was purified by reverse phase preparative HPLC. 131 mg (0.37 mmol) of the desired compound were obtained.

Intermediate 39a

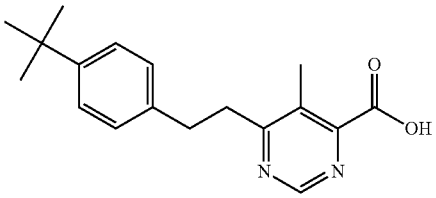
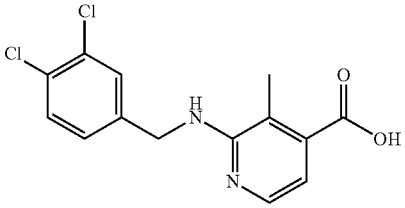
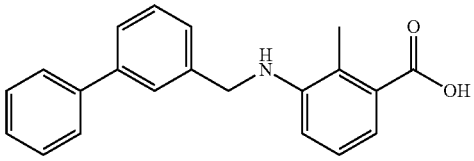


Intermediate 35 (300 mg, 0.92 mmol) was dissolved in 4 ml of ethanol and 4 ml of water. Lithium hydroxide (194 mg, 4.7 mmol) was added and the reaction mixture was stirred at 70° C. for 2 h, concentrated under vacuum and the remaining aqueous solution was acidified by 10 ml of a 4M solution of hydrochloric acid in 1,4-dioxane and extracted with dichloromethane; the organic phase was separated, washed with brine, dried over sodium sulfate and concentrated under vacuum. 250 mg (0.84 mmol) of the desired product were obtained.

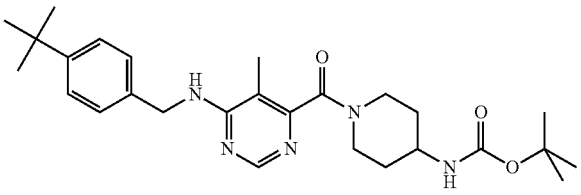
The following intermediates were synthesized in analogy to intermediate 39a

Ester Intermediate	Acid Intermediate	STRUCTURE
33	39b	

-continued

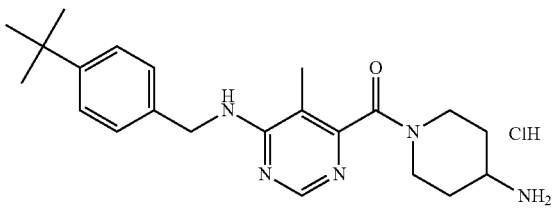
Ester Intermediate	Acid Intermediate	STRUCTURE
36	39c	
37	39d	
38	39e	

Intermediate 40a



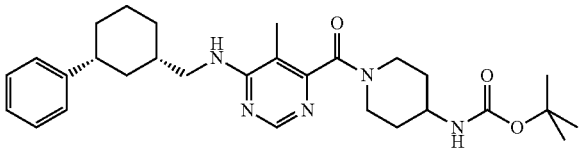
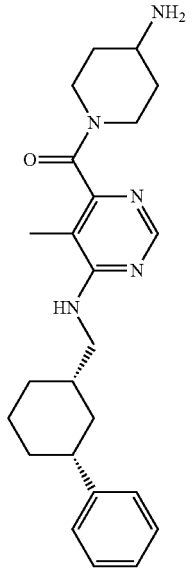
Intermediate 27c (660 mg, 2.20 mmol), TBTU (849 mg, 2.65 mmol) and N,N-diisopropylethylamine (0.57 ml, 3.31 mmol) were dissolved in 25 ml DMF. The reaction mixture was stirred under nitrogen atmosphere at room temperature for 10 min; then piperidin 4-yl carbamic acid tert-butyl ester (441 mg, 2.20 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with dichloromethane and washed with an aqueous saturated solution of sodium bicarbonate. The organic phase was separated, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Biotage SNAP column 50 g; eluent: dichloromethane/methanol=90/10%). 990 mg (2.05 mmol) of the desired compound were obtained.

Intermediate 41a

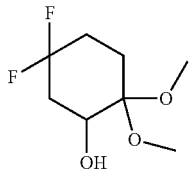


Intermediate 40a (990 mg, 2.05 mmol) was suspended in 50 ml of 1,4-dioxane, a 4M solution of hydrochloric acid (8.5 ml, 34 mmol) in 1,4-dioxane was added dropwise. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated under vacuum. 780 mg (18 mmol) of the desired compound were obtained.

The following intermediates were synthesized in analogy to Intermediates 40a and 41a.

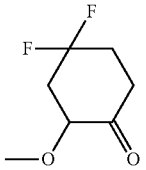
Starting acid	Starting amine	Carbamate Intermediate	STRUCTURE	Amine intermediate	STRUCTURE
Intermediate 27ha	piperidin 4-yl carbamic acid tert-butyl ester	40b		41b	ClH 

Intermediate 42



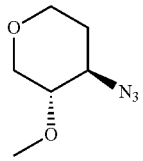
4,4-Difluorocyclohexanone (500 mg, 3.73 mmol) and potassium hydroxide (502 mg, 8.95 mmol) were dissolved in 10 ml of methanol. The reaction mixture was cooled to 0° C. and a solution of iodine (1.04 g, 4.10 mmol) in 20 ml of methanol was added dropwise within 1 h. The reaction mixture was stirred at room temperature for 18 h, and then concentrated under vacuum. The crude product was stirred in 10 ml of dichloromethane and the precipitate was filtered off. The filtrate was concentrated under vacuum and 480 mg of the desired product (2.45 mmol) were obtained as an oil.

Intermediate 43



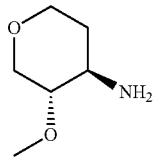
Sodium hydride (196 mg, 4.89 mmol) was suspended in 10 ml of tetrahydrofurane. The reaction mixture was cooled to 0° C. and a solution of Intermediate 42 (480 mg, 4.45 mmol) in 5 ml of tetrahydrofurane was added dropwise. The reaction mixture was stirred at 0° C. for 1 h, then iodomethane (0.305 ml, 4.89 mmol) was added. The reaction mixture was stirred at room temperature for 4 h. 0.1 ml of a 37% aqueous solution of hydrochloric acid and 0.1 ml of water were added, then additional 0.3 ml of a 37% aqueous solution of hydrochloric acid were added. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated under vacuum and 400 mg (2.44 mmol) of the desired product were obtained as an oil.

Intermediate 44



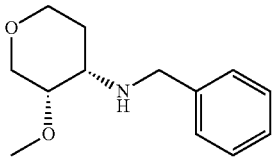
Iodomethane (3.48 ml, 55.88 mmol) was dissolved in 250 ml of tetrahydrofurane, the reaction mixture was stirred at 0° C. under nitrogen atmosphere and sodium hydride (60% on mineral oil, 2.23 mg, 5.88 mmol) was added. After 15 minutes, trans 4-azido-tetrahydropyran-3-ol (4.0 g, 27.94 mmol) was added and the reaction mixture was allowed to reach room temperature and stirred for 18 h. 50 ml of water were added, the organic phase was separated, dried over sodium sulphate and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (Biotage SNAP column 100 g; eluent: dichloromethane/ethyl acetate=80/20%). 200 mg (1.27 mmol) of the desired regioisomer were obtained as trans racemate (relative configuration assigned by NMR).

Intermediate 45



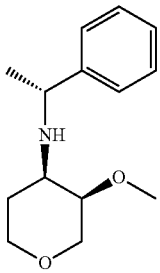
Intermediate 44 (200 mg, 1.27 mmol) was dissolved in 250 ml of methanol, Pd/C (50 mg was added and the reaction mixture was stirred under hydrogen atmosphere (4 bar) for 18 h. The reaction mixture was filtered on a celite pad and the organic phase was concentrated under vacuum. 110 mg (0.84 mmol) of the desired product were obtained as trans racemate.

Intermediate 46a



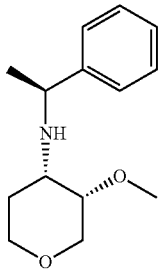
3-Methoxy-tetrahydro-pyran-4-one (500 mg, 3.84 mmol), benzylamine (0.42 ml, 3.84 mmol) and Raney-Nickel (100 mg) were suspended in 20 ml of dry ethanol and the reaction mixture was stirred under hydrogen atmosphere (4.5 bar) for 3 days. The reaction mixture was filtered on a celite pad and the organic phase was concentrated under vacuum. The crude product obtained was dissolved in 10 ml of methanol, loaded on a SCX cartridge (10 g) and eluted with a 2M solution of ammonia in methanol. The solvent was concentrated under vacuum and the crude product obtained was purified by flash chromatography (Isolute cartridge 10 g; eluent: dichloromethane/methanol=96/4%). 163 mg (0.73 mmol) of the desired product were obtained as cis racemate (relative configuration assigned by NMR).

Intermediate 46b



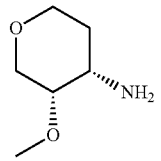
3-Methoxy-tetrahydro-pyran-4-one (1 g, 7.68 mmol), (R)-(+)-1-phenylethylamine (0.99 ml, 7.68 mmol) and Raney-Nickel (200 mg) in 10 ml dry ethanol were stirred under a hydrogen atmosphere (5 bar) for 15 days. The reaction mixture was diluted with 20 ml of methanol and 20 ml of tetrahydrofurane, stirred for 15 minutes, filtered on a celite pad and concentrated under vacuum. The crude product was loaded on a SCX cartridge (50 g). The cartridge was washed with methanol and the desired product was eluted with a 7 M solution of ammonia in methanol. The basic organic phase was concentrated under vacuum and the crude product obtained was purified by flash chromatography (dichloromethane/methanol=98/2%) to obtain 710 mg (3.02 mmol) of the desired product as single stereoisomer (diastereoisomeric purity confirmed and relative cis stereochemistry assigned by NMR).

Intermediate 46c



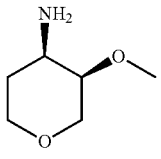
was synthesised in analogy to Intermediate 46b, starting from 3-Methoxy-tetrahydro-pyran-4-one and (S)-(−)-1-phenylethylamine (diastereoisomeric purity confirmed and relative cis stereochemistry assigned by NMR).

Intermediate 47a



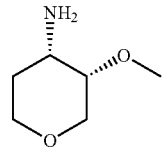
Intermediate 46a (163 mg, 0.73 mmol) was dissolved in 10 ml of methanol, Pd/C (50 mg) was added and the reaction mixture was stirred under hydrogen atmosphere (4.5 bar) for 18 h. The reaction mixture was filtered on a celite pad and the organic phase was concentrated under vacuum. 80 mg (0.61 mmol) of the desired product were obtained as cis racemate.

Intermediate 47b



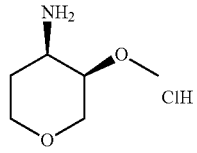
Intermediate 46b (1.18 g, 5.01 mmol), Pd/C 10% (200 mg) and acetic acid (0.3 ml, 5.01 mmol) in 20 ml of methanol were stirred under a hydrogen atmosphere (5 bar) for 18 h. The reaction mixture was diluted with 20 ml of methanol, stirred for 15 minutes, filtered on a celite pad and concentrated under vacuum. The crude product was loaded on a SCX cartridge (50 g). The cartridge was washed with methanol and the desired product was eluted with a 7 M solution of ammonia in methanol. The basic organic phase was concentrated under vacuum and 513 mg (3.91 mmol) of the desired product were obtained as single stereoisomer.

Intermediate 47c



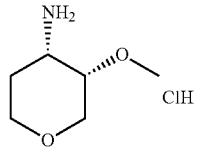
was synthesised in analogy to Intermediate 47b, starting from Intermediate 46c

Intermediate 48b



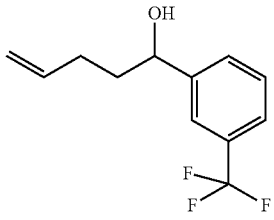
Intermediate 47b was stirred in diethyl ether and a 2M solution of hydrochloric acid in diethyl ether was added dropwise until a white solid was formed. The reaction mixture was concentrated under vacuum, the crude product was suspended in methanol and the reaction mixture was concentrated under vacuum to give the desired hydrochloride.

Intermediate 48c



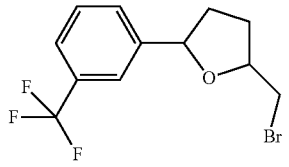
was synthesised in analogy to Intermediate 48b, starting from Intermediate 47c.

Intermediate 49a



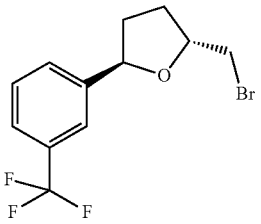
3-(trifluoromethyl)benzaldehyde (6.46 ml, 48.24 mmol) was dissolved in 80 ml of dry tetrahydrofurane, the reaction mixture was cooled to −78° C. and a 0.5M solution of 3-butenylmagnesiumbromide in tetrahydrofurane (106.13 ml, 53.06 mmol) was added dropwise over 30 minutes. The reaction mixture was stirred at −78° C. for 30 minutes. Then, the reaction mixture was allowed to reach room temperature and stirred 18 h. Then, 100 ml of a saturated aqueous solution of ammonium chloride and 200 ml of ethyl acetate were added. the organic layer was separated, dried over sodium sulfate and concentrated under vacuum. 7.75 g (33.69 mmol) of the desired product were obtained.

Intermediate 50a



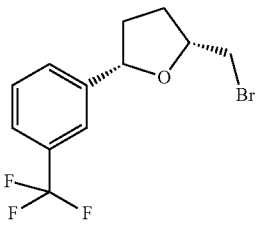
Intermediate 49a was dissolved in 70 ml of dry dichloromethane, the reaction mixture was stirred under nitrogen atmosphere at 0° C. and N-bromosuccinimide was added. The reaction mixture was allowed to reach room temperature and stirred for 48 h. The reaction mixture was concentrated under vacuum. The crude product was purified by flash chromatography (Isolera cartridge eluent: hexane/ethyl acetate=90/10%) to obtain the desired product as diastereoisomeric mixture.

Intermediate 51a



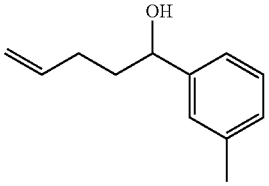
Intermediate 50a was purified by flash chromatography (Isolera cartridge; eluent: hexane/ethyl acetate=98/2%). 2.3 g (7.44 mmol) of the trans diastereoisomer were obtained as racemic mixture (relative stereochemistry assigned by NMR).

Intermediate 52a



Further elution of the column gave 1.05 g (3.39 mmol) of the cis diastereoisomer as racemic mixture (relative stereochemistry assigned by NMR).

The following intermediates were synthesized in analogy to Intermediates 49a, 50a, 51a and 52a

Starting aldehyde	Intermediate	STRUCTURE
3-Methyl-benzaldheyde	49b	

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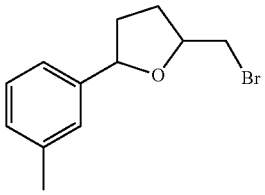
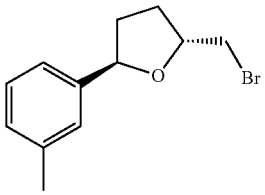
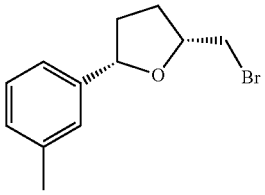
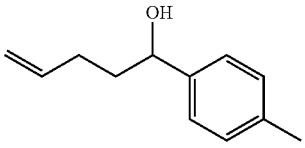
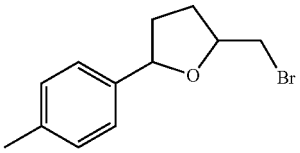
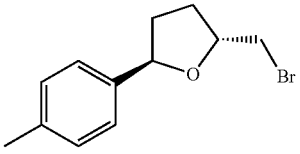
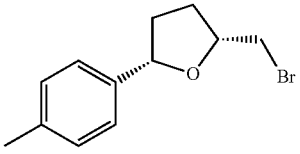
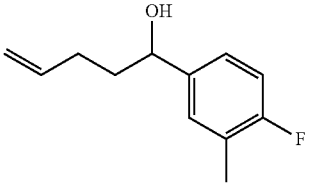
Starting aldehyde	Intermediate	STRUCTURE
	50b	
	51b	
	52b	
4-Methyl-benzaldheyde	49c	
	50c	
	51c	
	52c	
4-Fluoro-3-methyl-benzaldheyde	49d	

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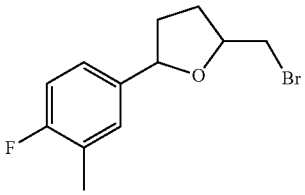
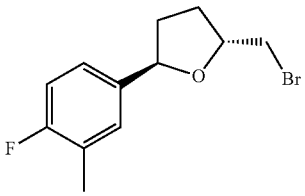
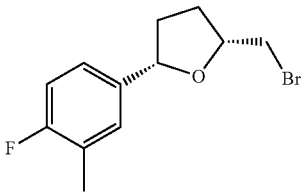
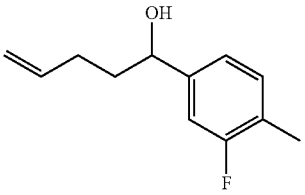
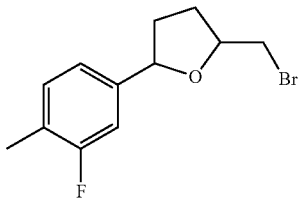
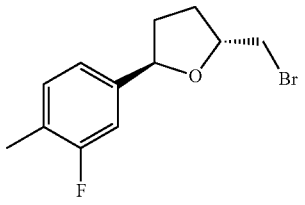
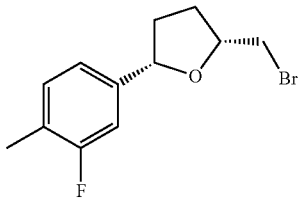
Starting aldehyde	Intermediate	STRUCTURE
	50d	
	51d	
	52d	
3-Fluoro-4-methyl-benzaldheyde	49e	
	50e	
	51e	
	52e	

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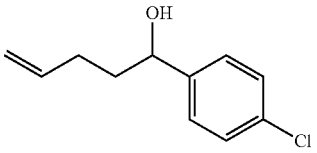
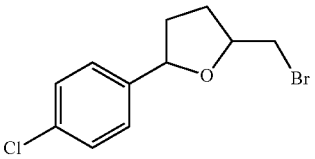
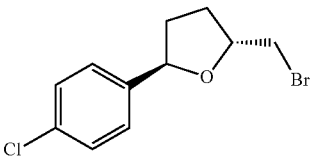
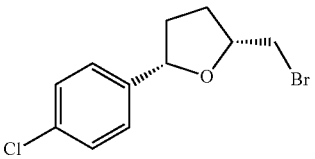
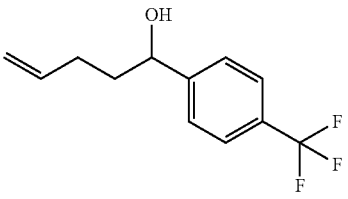
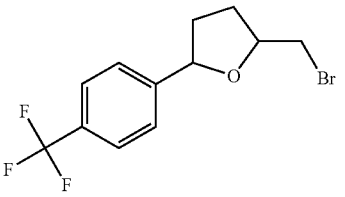
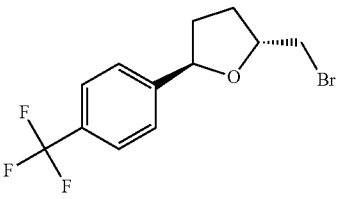
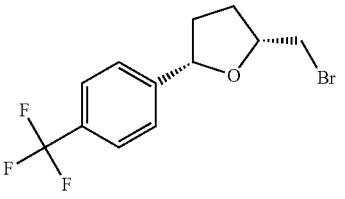
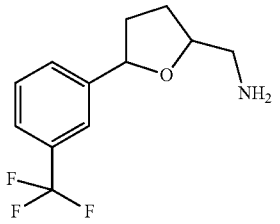
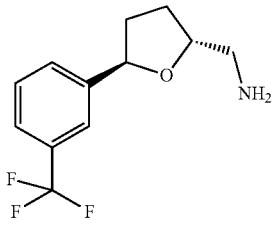
Starting aldehyde	Intermediate	STRUCTURE
4-Chloro-benzaldheyde	49f	
	50f	
	51f	
	52f	
4-Trifluoro-methyl-benzaldheyde	49g	
	50g	
	51g	
	52g	

Intermediate 53a



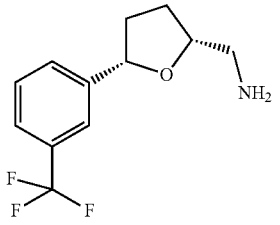
Intermediate 50a (1.7 g, 5.49 mmol) was dissolved in 5 ml of DMSO and the reaction mixture was stirred under nitrogen atmosphere at room temperature. Phthalimide potassium salt (2.54 g, 13.75 mmol) and sodium iodide (240 mg, 1.60 mmol) were added and the reaction mixture was stirred at 70° C. for 18 h. The reaction mixture was cooled to room temperature and diluted with 40 ml of a saturated aqueous sodium bicarbonate solution and with 100 ml of ethyl acetate. The organic layer was separated, dried on sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Isolera cartridge; eluent: hexane/ethyl acetate=85/15%) to yield 1.2 g (3.2 mmol) of the phthalimido intermediate. The phthalimido intermediate (1.2 g, 3.2 mmol) was dissolved in 15 ml of methanol. Hydrazine hydrate (1.24 ml, 25.60 mmol) was added and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was concentrated under vacuum. The crude product was dissolved in 10 ml of dichloromethane, the organic layer was washed with water, separated, dried on sodium sulfate and concentrate under vacuum. 474 mg (1.93 mmol) of the desired product were obtained.

Intermediate 54a



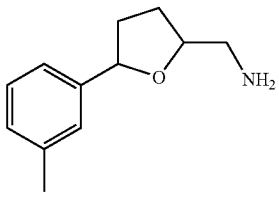
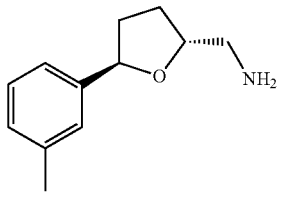
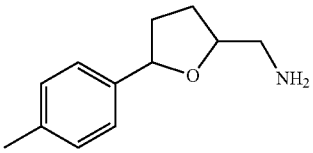
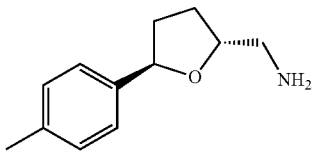
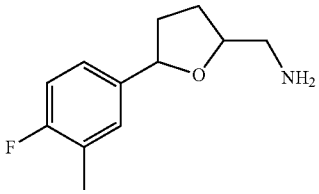
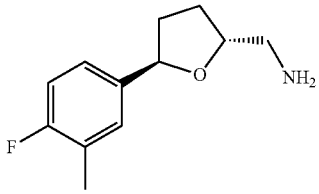
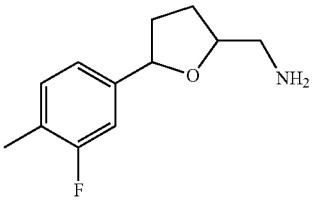
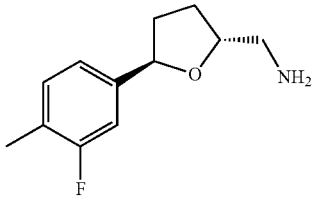
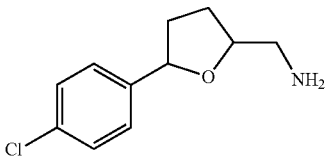
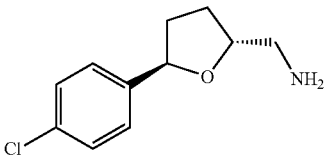
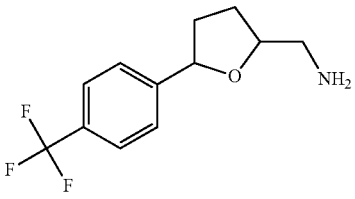
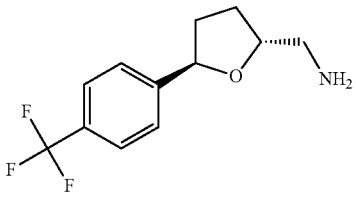
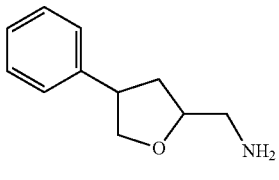
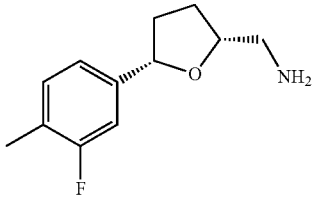
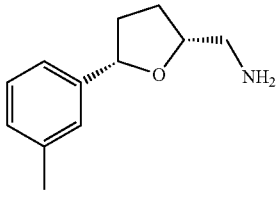
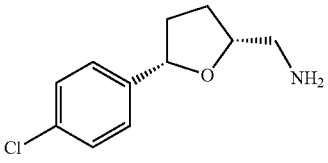
was synthesized in analogy to Intermediate 53a starting from intermediate 51a

Intermediate 55a



was synthesized in analogy to Intermediates 53a starting from intermediate 52a.

The following intermediates were synthesized in analogy to Intermediates 53a, 54a and 55a.

Starting Inter-mediate	Inter-mediate	STRUCTURE	Starting inter-mediate	Inter-mediate	STRUCTURE
50b	53b		51b	54b	
50c	53c		51c	54c	
50d	53d		51d	54d	
50e	53e		51e	54e	
50f	53f		51f	54f	
50g	53g		51g	54g	
2-bromo-methyl-4-phenyl-tetra-hydro-furan	53h		52e	55e	
52b	55b		52f	55f	

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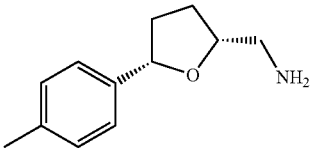
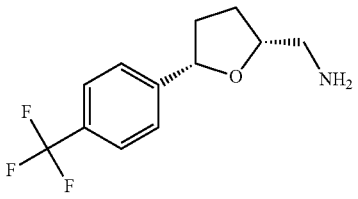
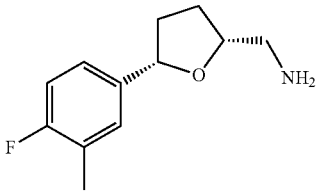
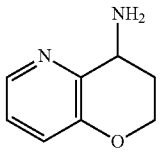
Starting Inter-mediate	Inter-mediate	STRUCTURE	Starting inter-mediate	Inter-mediate	STRUCTURE
52c	55c		52g	55g	
52d	55d				

Intermediate 56



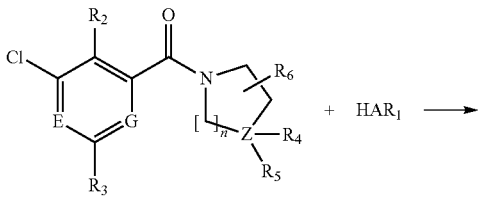
2,3-Dihydro-pyrano[3,2-b]pyridine-4one (250 mg, 1.7 mmol) and Raney-Nickel (25 mg) were added to a solution of ammonia in ethanol (10 ml) and the reaction mixture was stirred under hydrogen atmosphere (3 bar) for 18 h at room temperature. Then, the catalyst was removed by filtration on a celite pad and the mixture was concentrated under vacuum. The residue was purified by reversed phase HPLC to give the desired product (129 mg, 600 μmol).

SYNTHESIS OF EXAMPLES

E and G within the scope of this invention denotes C or N, preferred nitrogen.

The examples of this invention are synthesized according to the following general synthetic procedures:

Synthetic Procedure A



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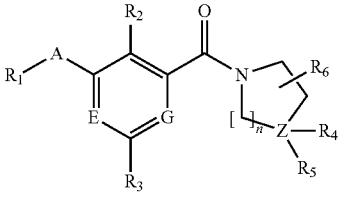
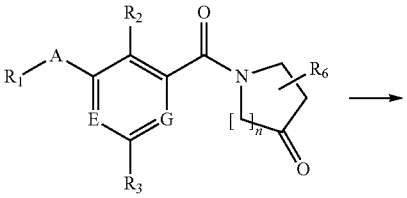
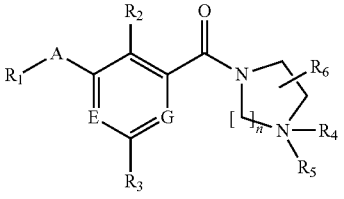


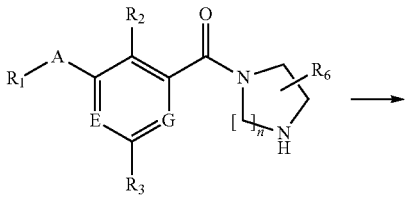
Examples: 1-159gc; 289-302

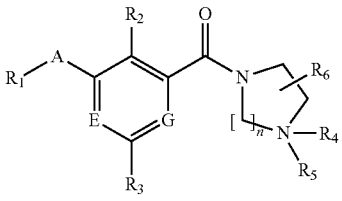
Synthetic Procedure B



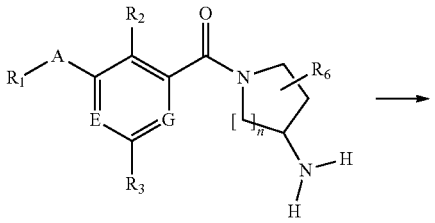


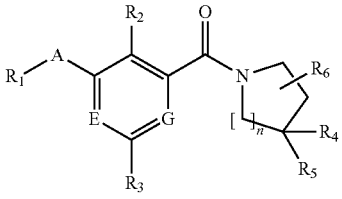
Examples: 160-247; 228a; 228ga-228gn; 229-247





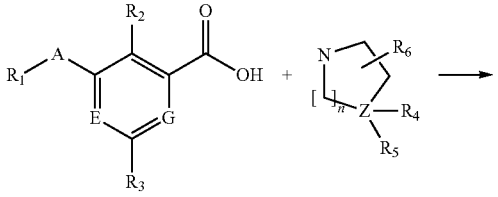
Examples: 286-288





Examples: 228b-228g; 228go; 228gp

Synthetic Procedure C



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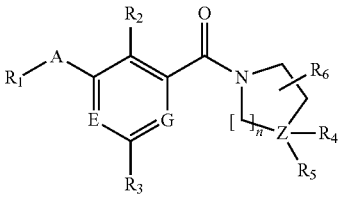
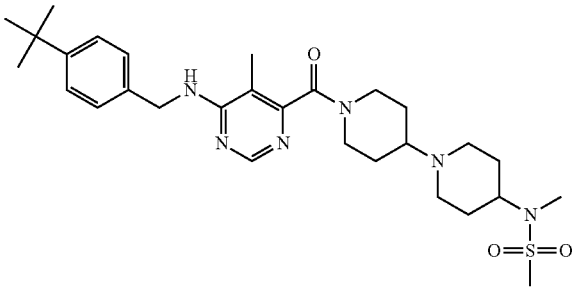


Examples: 248-283; 275a-275dj



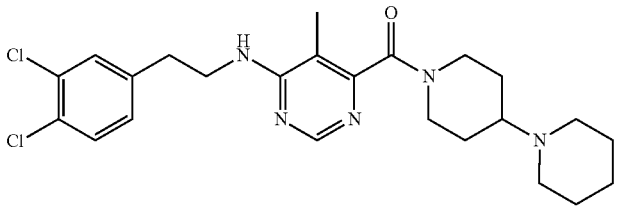
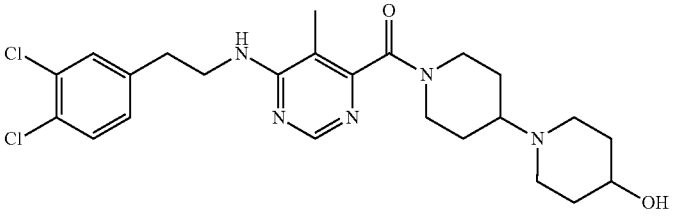
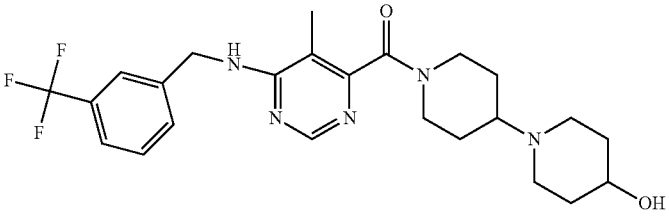
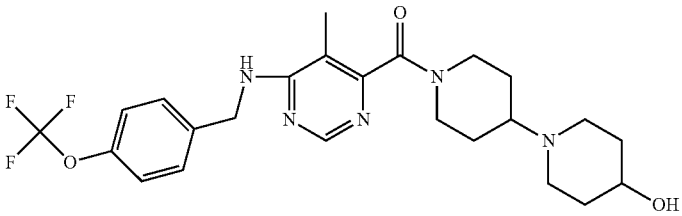
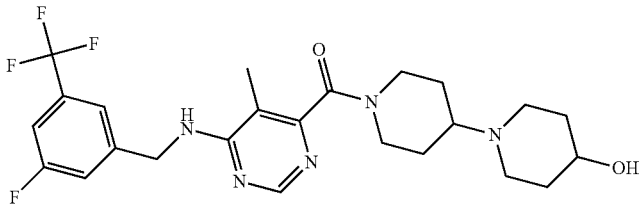
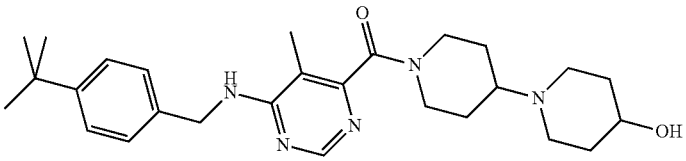
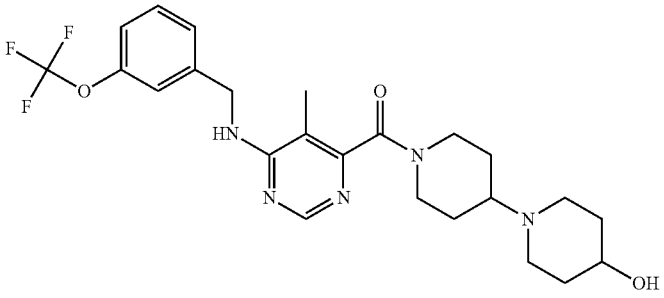
Example 1

Intermediate 25b (70 mg, 0.16 mmol), 4-tert-butyl-benzylamine (32 mg, 0.19 mmol) and N,N-diisopropyl-ethyl amine (0.042 ml, 0.24 mmol) in 2 ml of dry 1,4-dioxane were stirred at 70° C. overnight. The reaction mixture was concentrated under vacuum and the crude product was dissolved in dichloromethane. The organic phase was washed with a saturated aqueous sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Silica Isolute cartridge 5 g; eluent: ethyl acetate/methanol=90/10%). 16 mg (0.027 mmol) of the desired product were obtained.

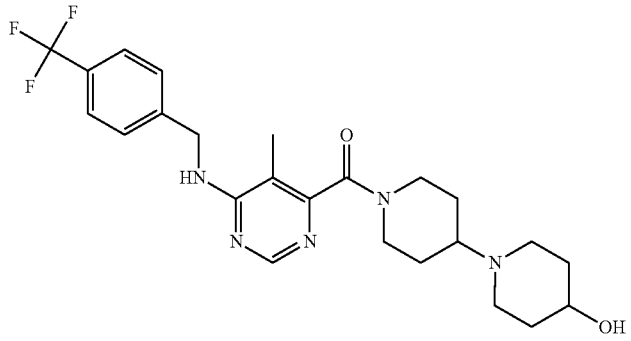
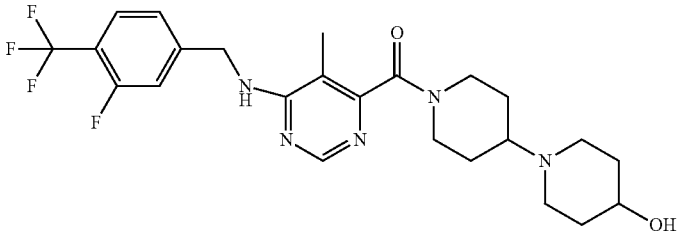
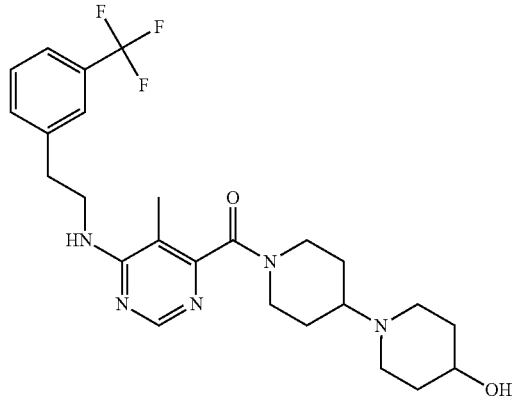
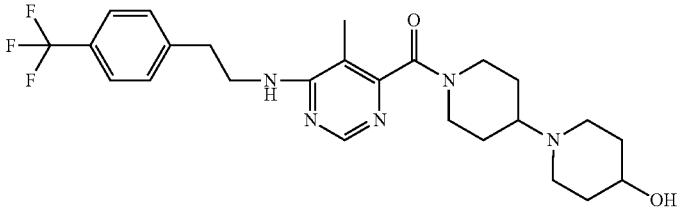
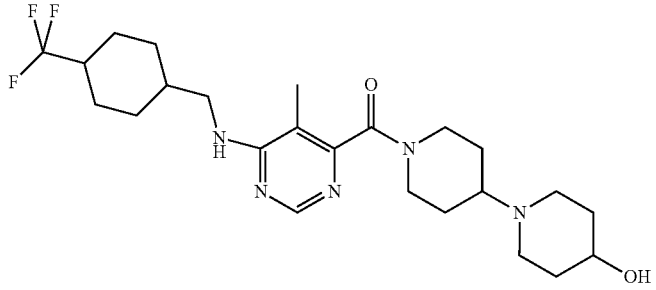
HPLC (Method 2F): R_t. (min)=7.59

$[M+H]^+$=557

The following examples were synthesized in analogy to the preparation of Example 1.

Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R_t,(min)	Meth-od
2		25i	2-(3,4-dichloro-phenyl)-ethyl-amine	476	7.98	1E
3		25f	2-(3,4-dichloro-phenyl)-ethyl-amine	492	2.91	B
4		25f	3-trifluoro methyl-benzyl-amine	478	6.77	1E
5		25f	4-trifluoro-methoxy-benzyl-amine	494	6.78	1E
6		25f	3-fluoro-5-trifluoro methyl-benzyl-amine	496	6.73	1E
7		25f	4-tert-butyl-benzyl-amine	466	7.45	1E
8		25f	3-trifluoro methoxy-benzyl-amine	494	7.08	1E

-continued

Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R_t-(min)	Meth-od
9		25f	4-trifluoro methyl-benzyl-amine	478	6.63	1E
10		25f	3-fluoro-4-trifluoro methyl-benzyl-amine	496	6.85	1E
11		25f	2-(3-trifluoro methyl-phenyl)-ethyl-amine	492	7.23	1E
12		25f	2-(4-trifluoro methyl-phenyl)-ethyl-amine	492	7.37	1E
13		25f	(4-(trifluoro-methyl)-cyclo-hexyl)-methan-amine	484	6.82	1E

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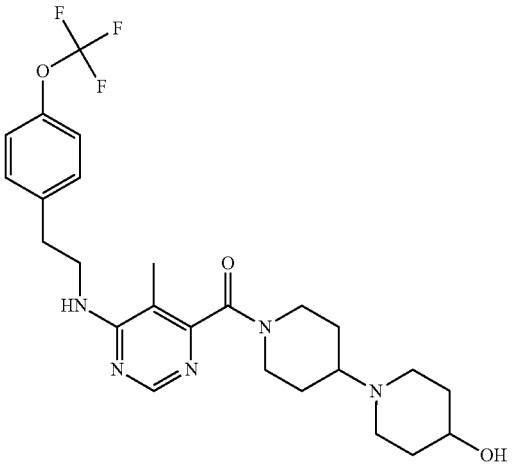
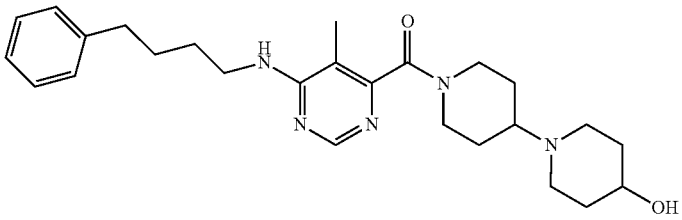
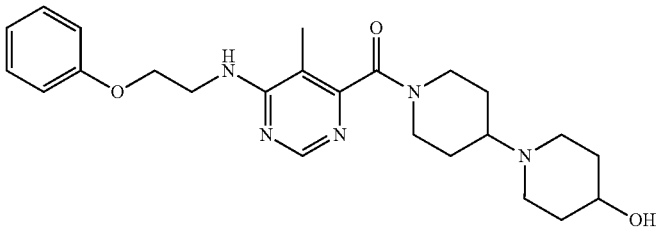
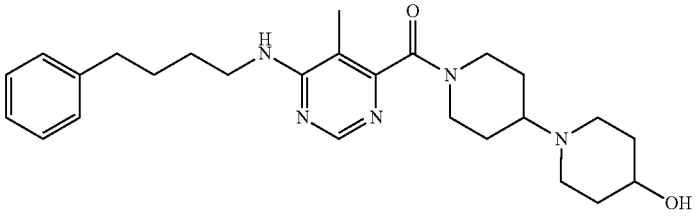
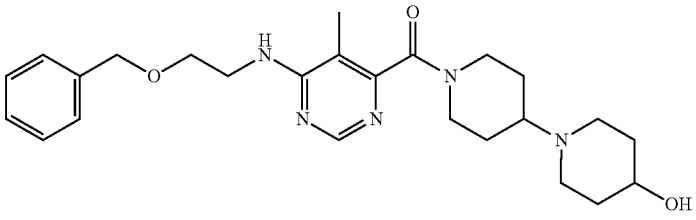
Ex #	STRUCTURE	Inter-me-diate	Amine	[M + H]$^+$	HPLC R_t-(min)	Meth-od
14		25f	2-(4-trifluoro-methoxy-phenyl)-ethyl-amine	508	7.37	1E (Fu-sion)
15		25f	4-phenyl-butyl-amine	452	7.15	1E
16		25f	2-phenoxy-ethyl-amine	440	7.10	1E (Fu-sion)
17		25f	3-phenyl-propyl-amine	438	7.83	1E (Fu-sion)
18		25f	2-benzyl-oxy-ethyl-amine	454	5.83	1E (Hydro)

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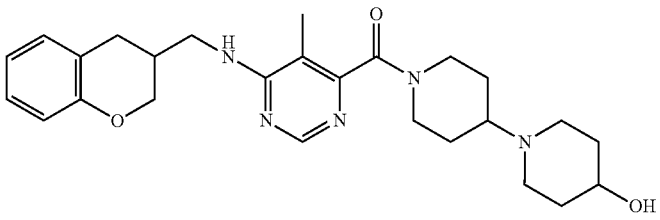
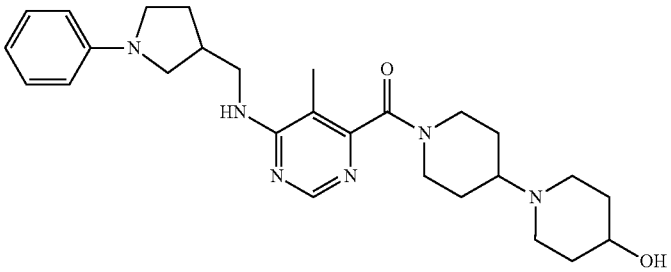
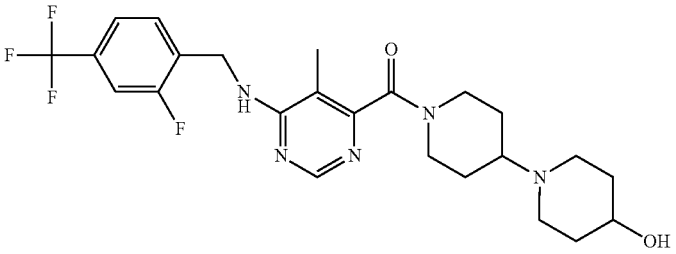
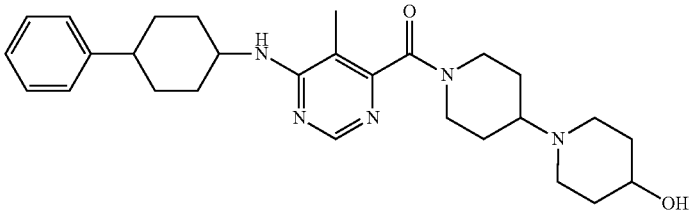
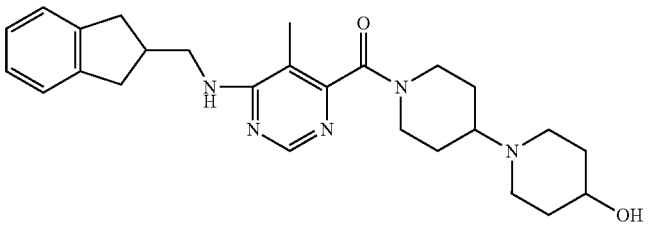
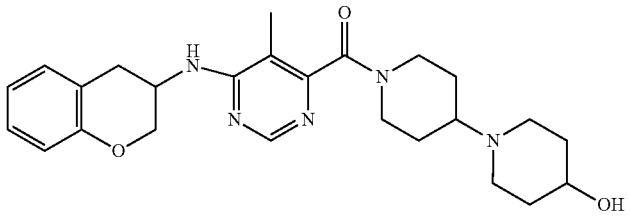
Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R_t-(min)	Meth-od
19		25f	chroman-3-yl-methan-amine	466	7.85	1E (Fu-sion)
20		25f	(1-phenyl-pyrroli-din-3-yl)-methan-amine	479	7.05	1E (Hydro)
21		25f	2-fluoro-4-tri-fluoro methyl-benzyl-amine	496	8.38	1E (Fu-sion)
22		25f	4-phenyl-cyclo-hexyl-amine	478	9.38	1E (Fu-sion)
23		25f	indan-2-yl-methan-amine	450	6.55	1E (Hydro)
24		25f	chroman-3-ylamine	452	6.18	1E (Hydro)

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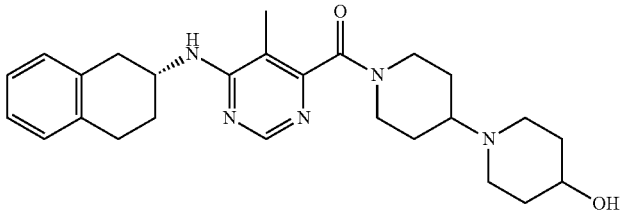
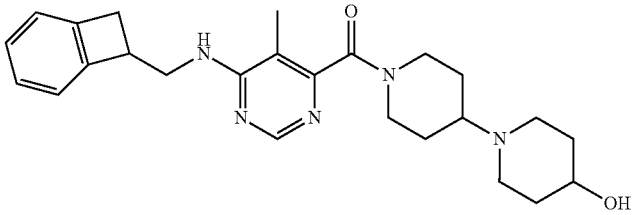
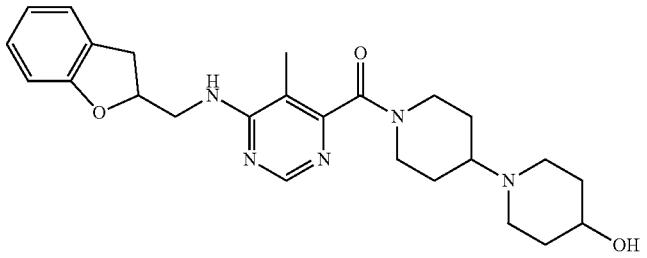
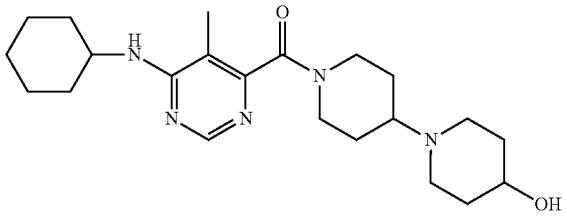
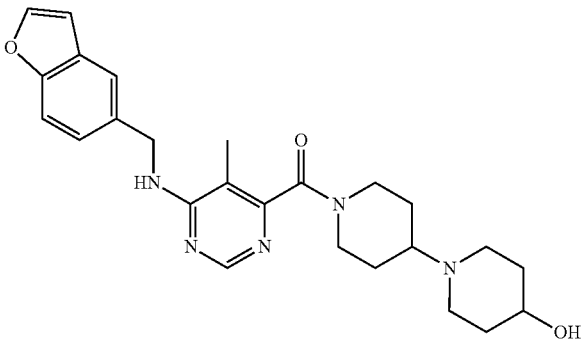
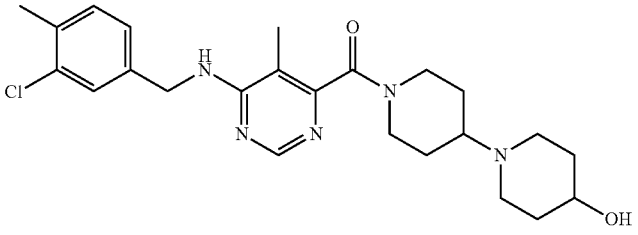
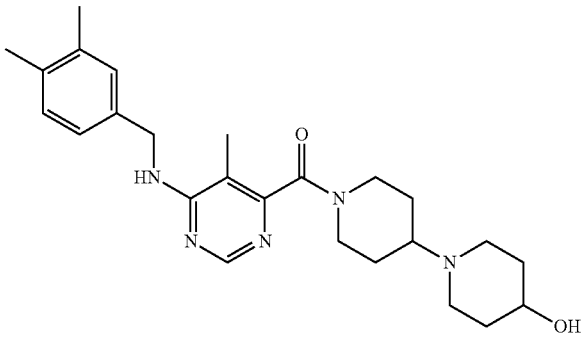
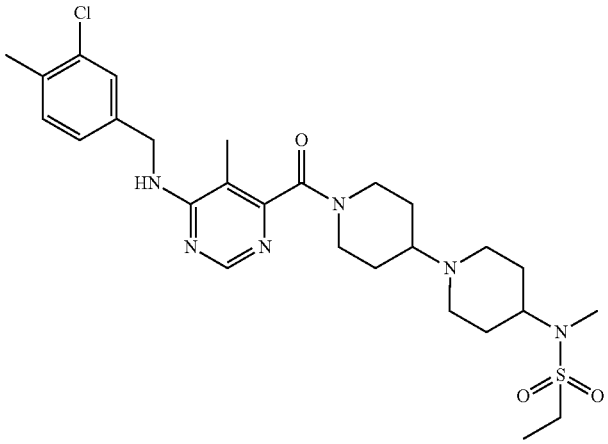
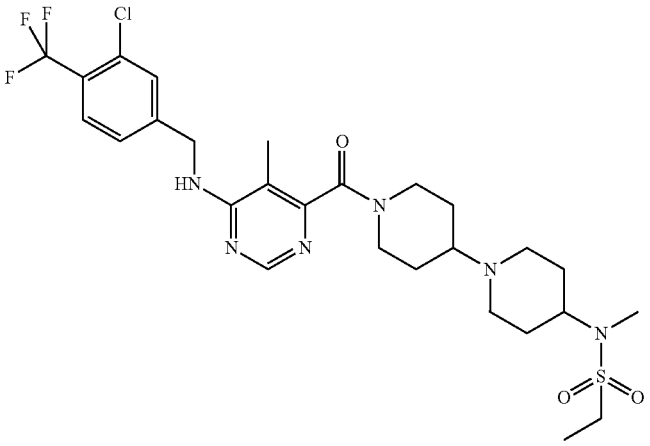
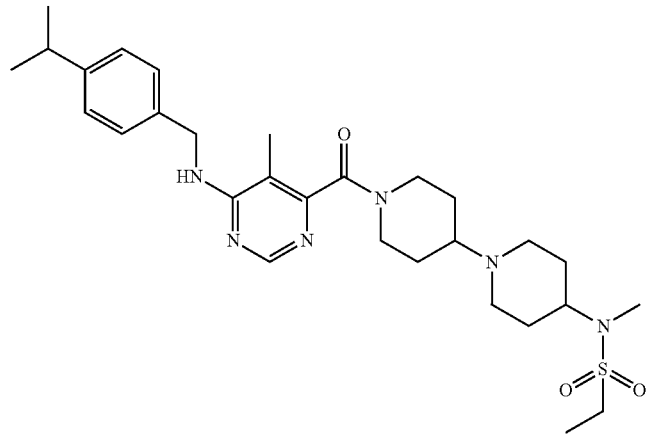
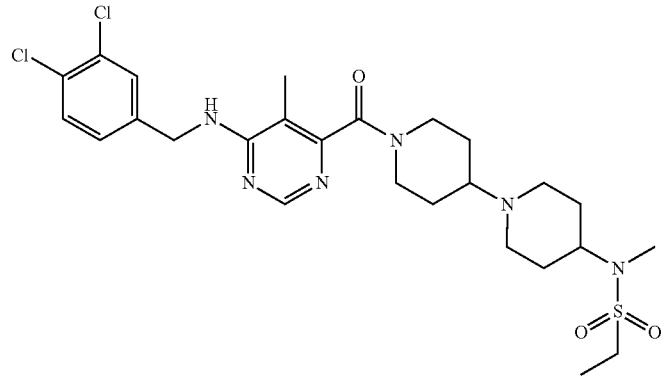
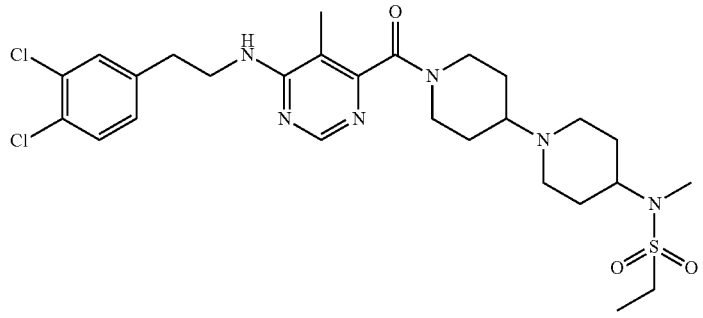
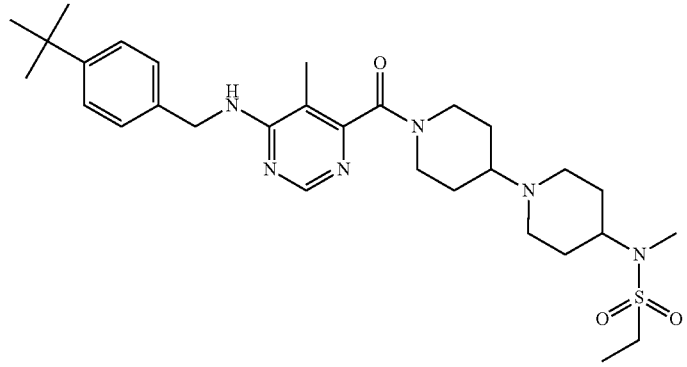
Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]$^+$	HPLC R_t-(min)	Meth-od
25		25f	(R)-(1,2,3,4-tetra-hydro-naphtalen-2-yl)amine	450	7.08	1E (Hydro)
26		25f	(1,2-di-hydro-cyclo-buta-benzen-1-yl)-methan-amide	436	6.93	1E (Hydro)
27		25f	(2,3-di-hydro-benzo-furan-2-yl)-methan-amine	452	6.47	1E (Hydro)
28		25f	Cyclo-hexyl-amine	402	4.90	1E
29		25f	benzo-furan-5-ylmethan amine	450	6.73	1E (Hydro)
30		25f	3-chloro-4-methyl-benzyl-amine	458	7.75	1E (Hydro)

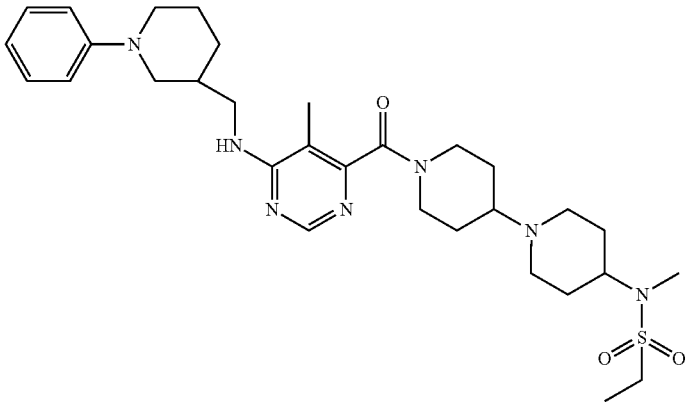
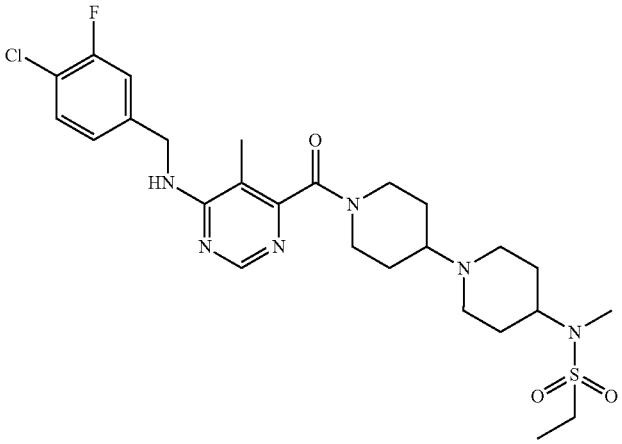
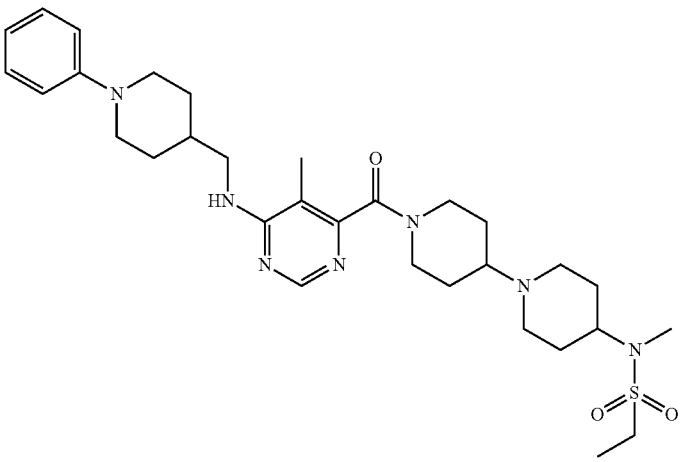
-continued

Ex #	STRUCTURE	Inter-me-diate	Amine	[M + H]+	HPLC R,-(min)	Meth-od
31		25f	3,4-di-methyl-benzyl-amine	438	7.37	1E (Hydro)
32		25c	3-chloro-4-methyl-benzyl-amine	563	6.98	2F
33		25c	3-chloro-4-tri-fluoro methyl-benzyl-amine	617	9.47	1E (Hydro)

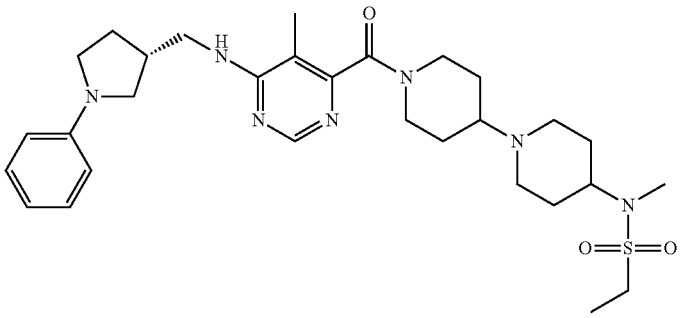
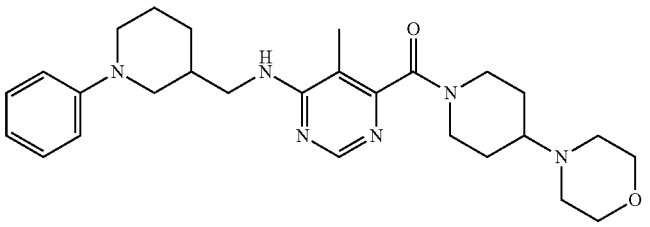
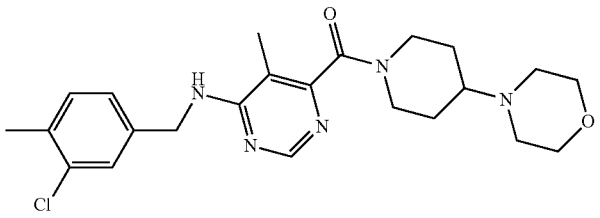
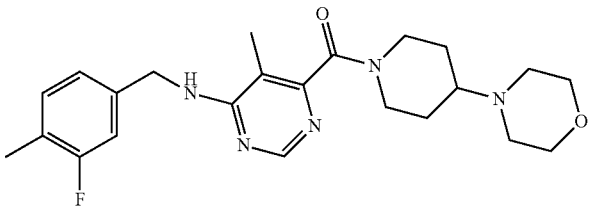
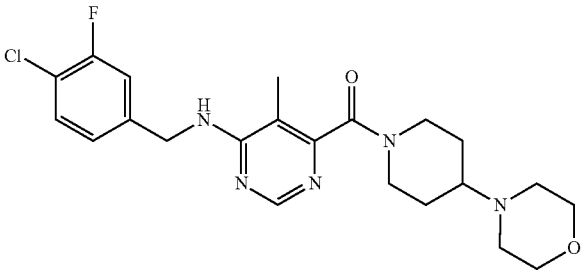
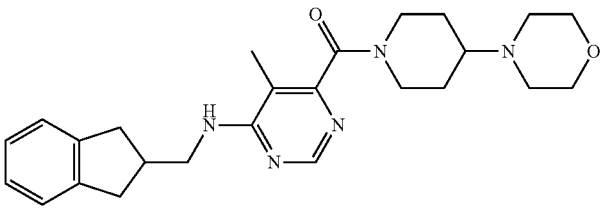
-continued

Ex #	STRUCTURE	Inter-me-diate	Amine	[M + H]+	HPLC R_t-(min)	Meth-od
34		25c	4-iso-propyl-benzyl-amine	557	7.03	2F
35		25c	3,4-di-chloro-benzyl-amine	583	8.65	1E (Hydro)
36		25c	2-(3,4-di-chloro-phenyl)-ethyl-amine	597	9.72	1E (Hydro)
37		25c	4-tert-butyl-benzyl-amine	571	9.28	1E (Hydro)

-continued

Ex #	STRUCTURE	Inter-me-diate	Amine	[M + H]$^+$	HPLC R_t-(min)	Meth-od
38		25c	9a	598	1.45	2F
39		25c	4-chloro-3-fluoro-benzyl-amine	567	8.82	1E (Hydro)
40		25c	(1-phenyl-piperidin-4yl)-methan-amine	598	8.98	1E (Hydro)

-continued

Ex #	STRUCTURE	Inter-me-diate	Amine	[M + H]+	HPLC R_t,(min)	Meth-od
41		25c	9b	584	8.92	1E (Hydro)
42		25h	9a	479	8.67	1E (Hydro)
43		25h	3-chloro-4-methyl-benzyl-amine	444	8.63	1E (Hydro)
44		25h	3-fluoro-4-methyl-benzyl-amine	428	7.58	1E (Hydro)
45		25h	4-chloro-3-fluoro-bemzyl-amine	448	7.88	1E (Hydro)
46		25h	indan-2yl-methan-amine	436	8.27	1E (Hydro)

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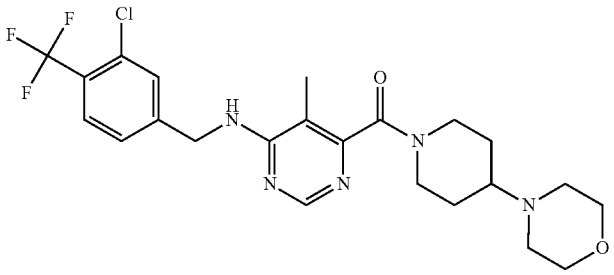
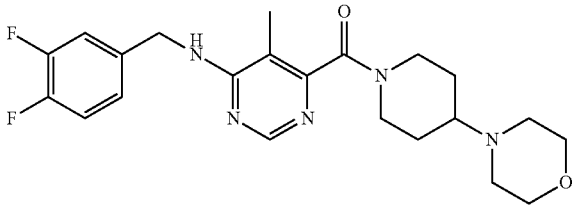
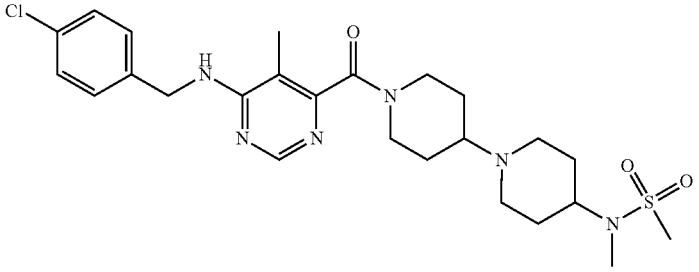
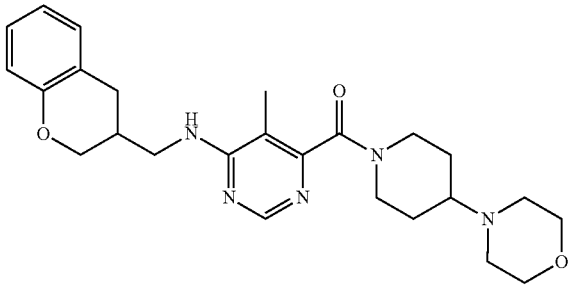
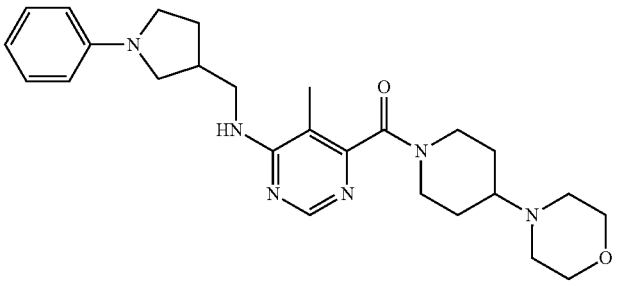
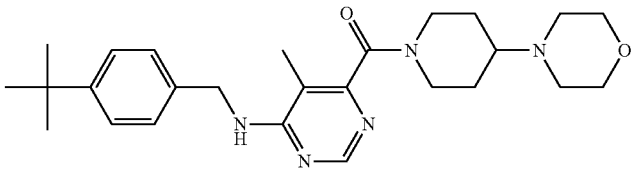
Ex #	STRUCTURE	Inter-me-diate	Amine	[M + H]+	HPLC R_t-(min)	Meth-od
47		25h	3-chloro-4-tri-fluoro methyl-benzyl-amine	498	7.30	2F
48		25h	3,4-difluoro-benzyl-amine	432	4.20	2G
49		25b	4-chloro-benzyl-amine	535	7.38	2F
50		25h	chroman-3-yl-methan amine	452	7.85	1E (Hydro)
51		25h	(1-phenyl-pyrroli-din-3-yl)-methan-amine	465	8.93	1E (Hydro)
52		25h	4-tert-butyl-benzyl-amine	452	7.18	2F

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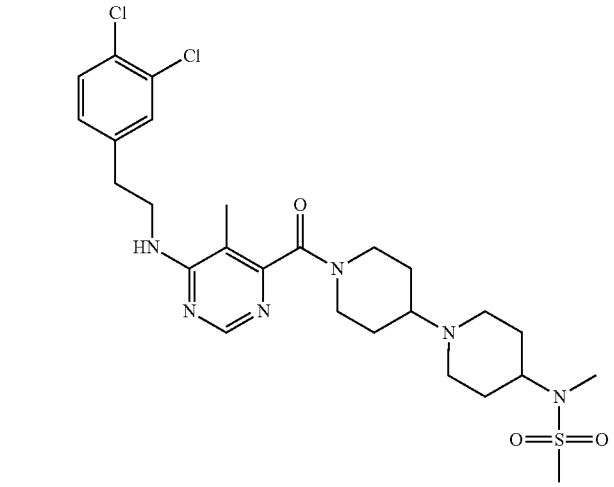
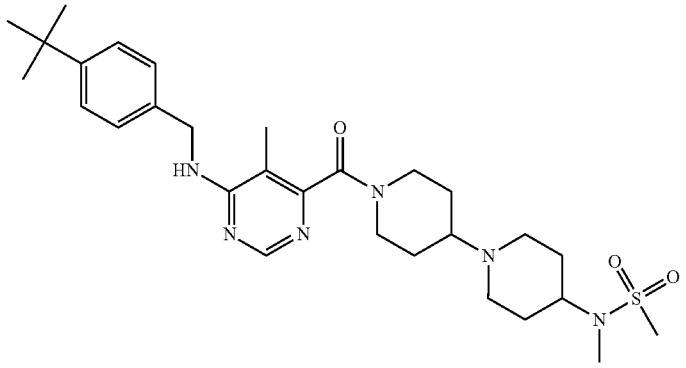
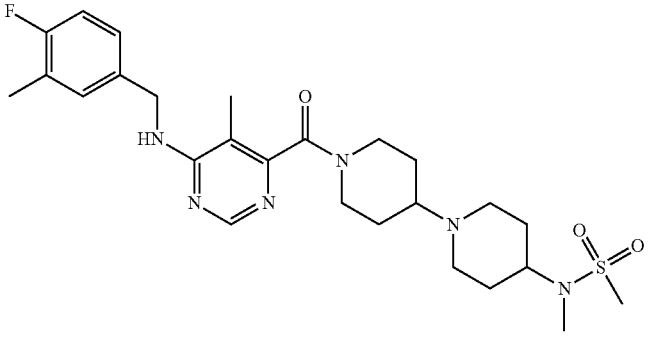
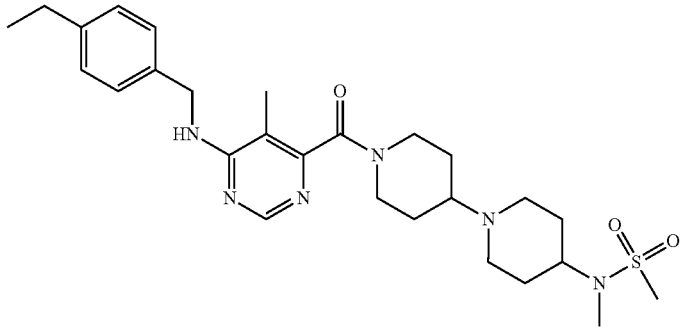
Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R_t-(min)	Meth-od
53		25b	2-(3,4-dichloro-phenyl)-ethyl-amine	583	7.97	1E (Hydro)
54		25b	(6-tert-butyl-pyridin-3-yl)-methan-amine	558	7.73	1E (Hydro)
55		25b	4-fluoro-3-methyl-benzyl-amine	533	8.05	1E (Hydro)
56		25b	4-ethyl-benzyl-amine	529	8.35	1E (Hydro)

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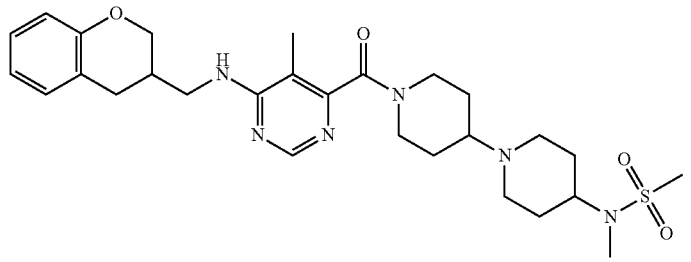
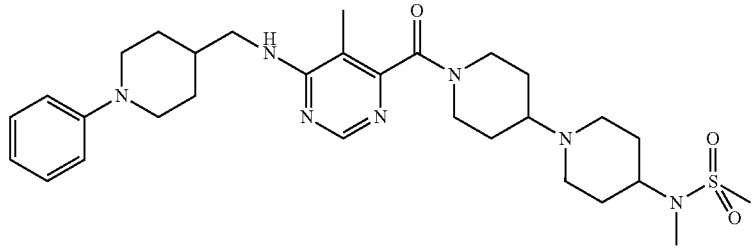
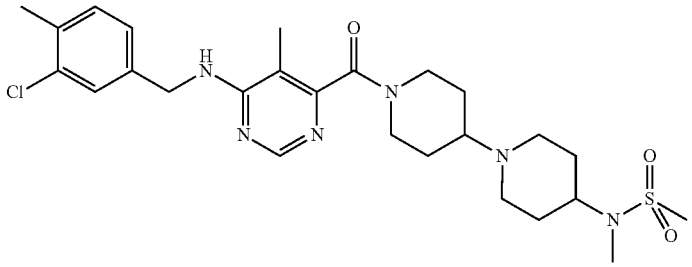
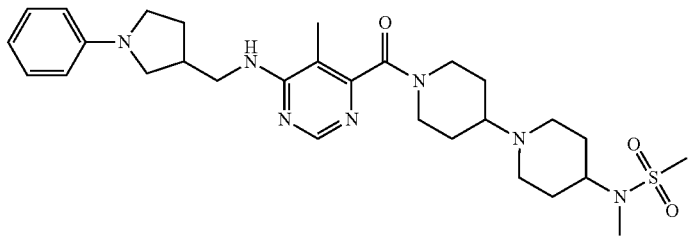
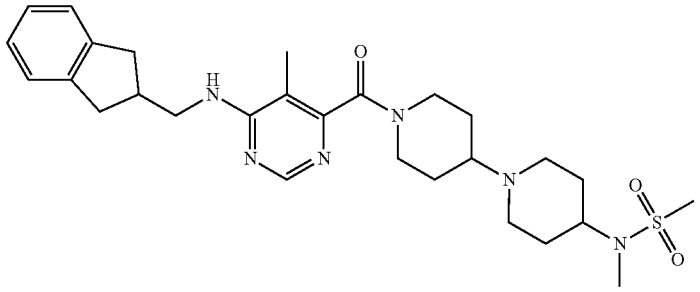
Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R_t-(min)	Meth-od
57		25b	chroman-3-yl-methan amine	557	7.62	1E (Hydro)
58		25b	(1-phenyl-piperidin-4yl)-methan-amine	584	8.05	1E (Hydro)
59		25b	3-chloro-4-methyl-benzyl-amine	549	8.22	1E (Hydro)
60		25b	(1-phenyl-pyrrolidin-3-yl)-methan-amine	570	8.07-8.47	1E (Hydro)
61		25b	indan-2yl-methan-amine	541	8.03	1E (Hydro)

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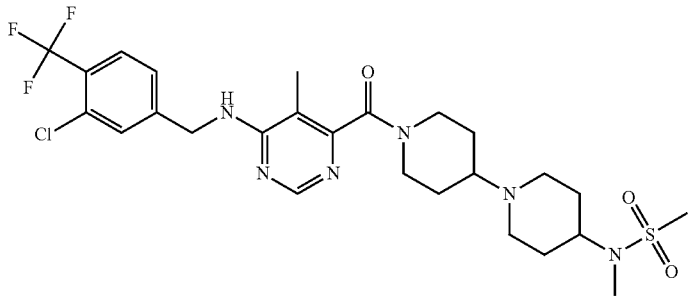
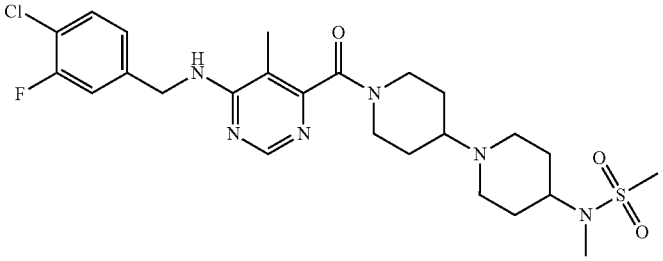
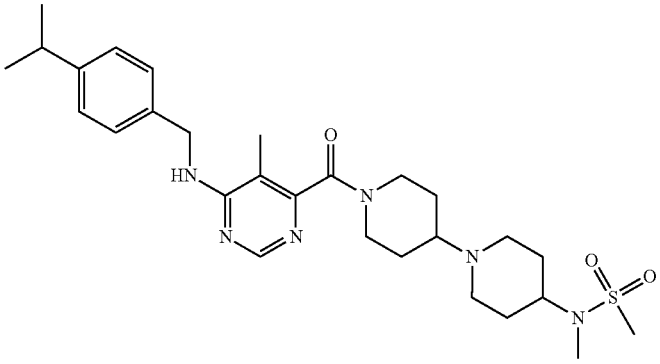
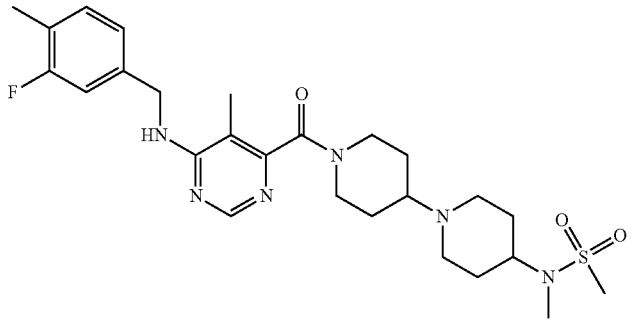
Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R_t-(min)	Meth-od
62		25b	3-chloro-4-tri-fluoro methyl-benzyl-amine	603	8.68	1E (Hydro)
63		25b	4-chloro-3-fluoro-benzyl-amine	553	7.55	1E (Hydro)
64		25b	4-iso-propyl-benzyl-amine	543	6.82	2F
65		25b	3-fluoro-4-methyl-benzyl-amine	533	8.57	1E (Hydro)

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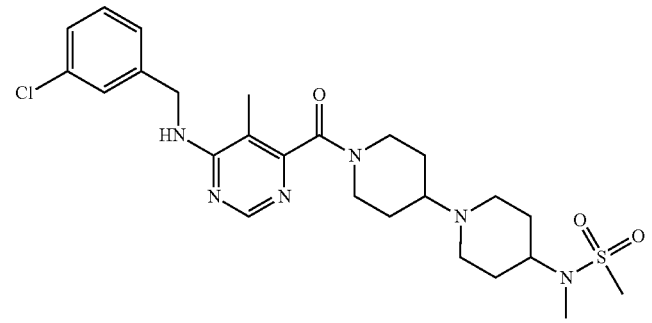
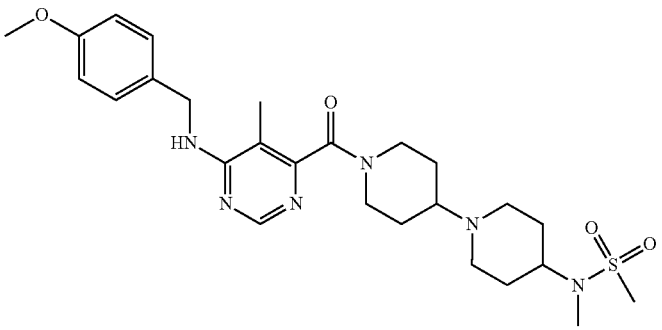
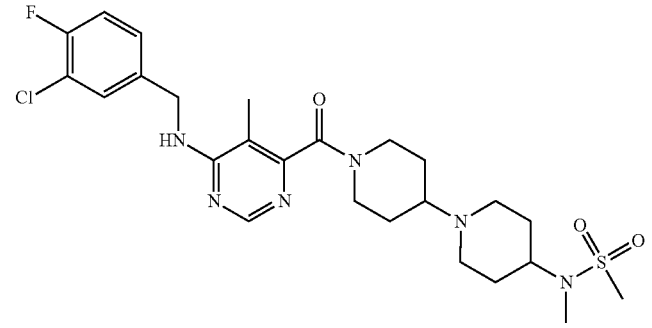
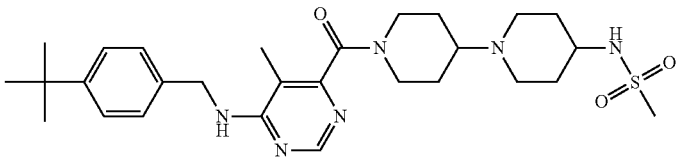
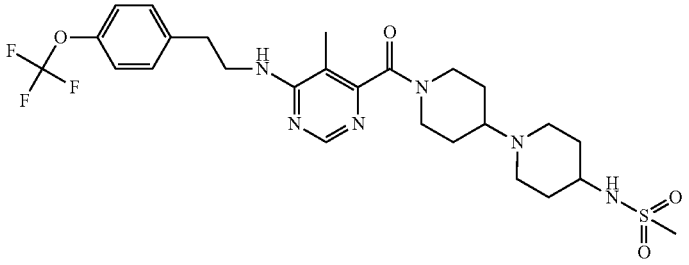
Ex #	STRUCTURE	Inter-me-diate	Amine	[M + H]+	HPLC R,-(min)	Meth-od
66		25b	3-chloro-benzyl-amine	535	6.72	2F
67		25b	4-methoxy-benzyl-amine	531	2.39	2F
68		25b	3-chloro-4-fluoro-benzyl-amine	553	7.57	2F
69		25a	4-tert-butyl-benzyl-amine	543	7.97	1E (Hydro)
70		25a	4-tri-fluoro methoxy-benzyl-amine	585	7.63	1E (Hydro)

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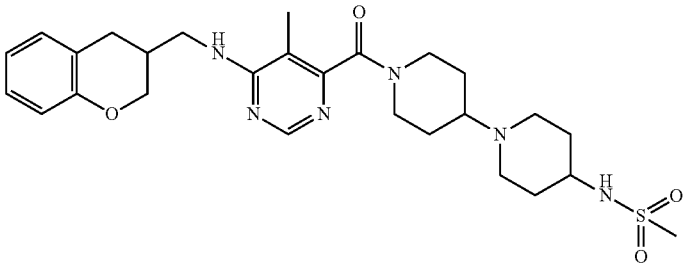
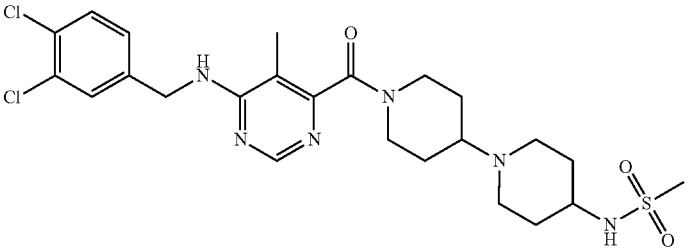
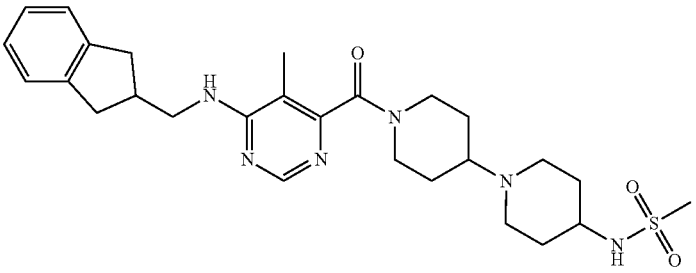
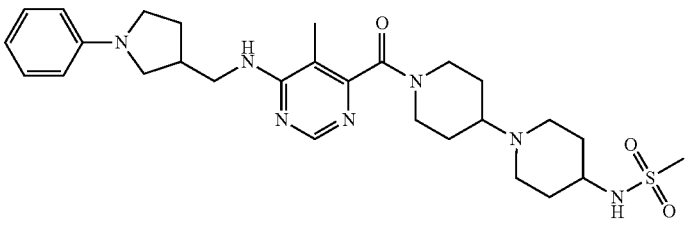
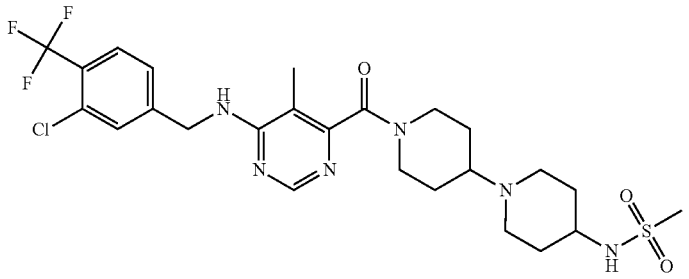
Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R,-(min)	Meth-od
71		25a	chroman-3-yl-methan amine	543	6.75	1E (Hydro)
72		25a	3,4-di-chloro-benzyl-amine	555	7.30	1E (Hydro)
73		25a	indan-2yl-methan-amine	527	7.35	1E (Hydro)
74		25a	(1-phenyl-pyrrolidin-3-yl)-methan-amine	555	7.43-7.80	1E (Hydro)
75		25a	3-chloro-4-tri-fluoro methyl-benzyl-amine	589	7.78	2F

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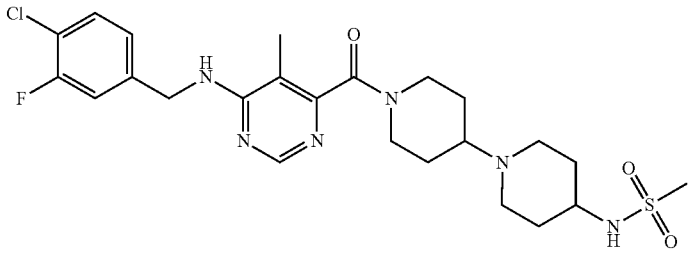
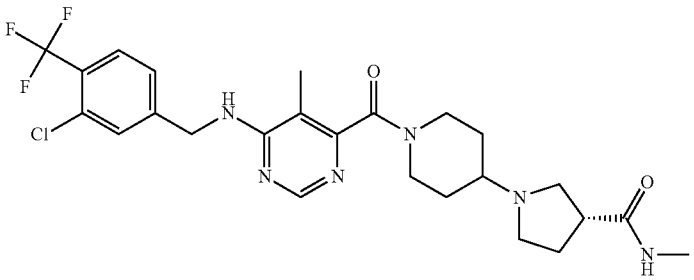
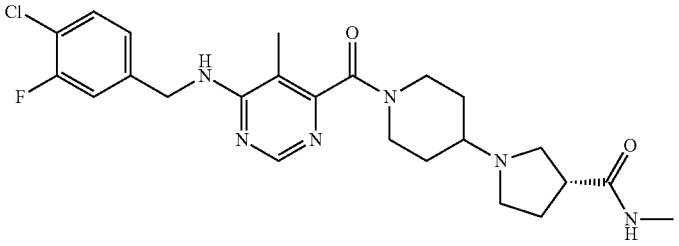
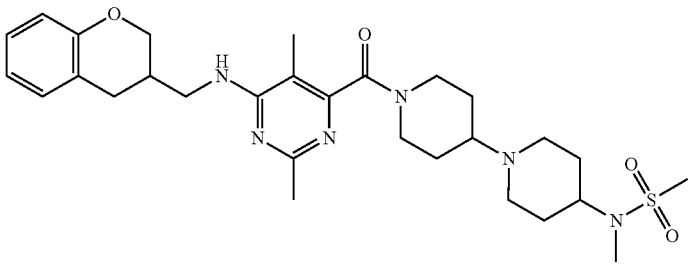
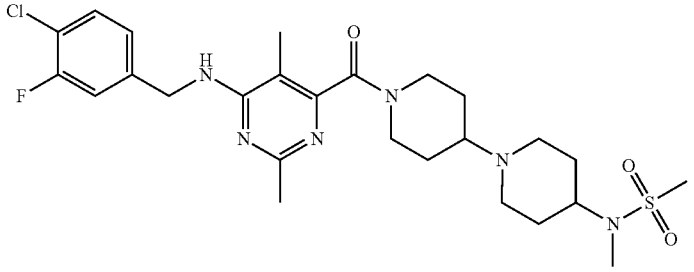
Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R_t-(min)	Meth-od
76		25a	4-chloro-3-fluoro-benzyl-amine	539	2.07	1F
77		25e	3-chloro-4-tri-fluoro methyl-benzyl-amine	539	8.23	1E (Hydro)
78		25e	4-chloro-3-fluoro-benzyl-amine	489	7.33	1E (Hydro)
79		25l	chroman-3-yl-methan amine	571	8.13	1E (Hydro)
80		25l	4-chloro-3-fluoro-benzyl-amine	567	8.36	1E (Hydro)

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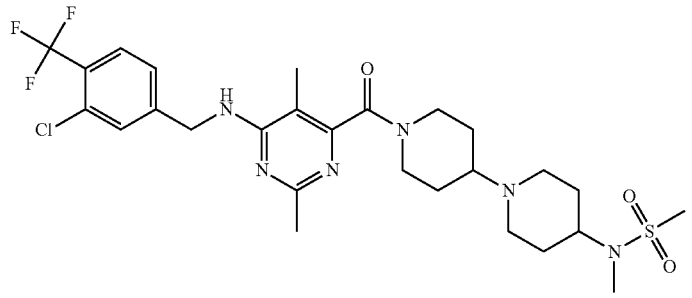
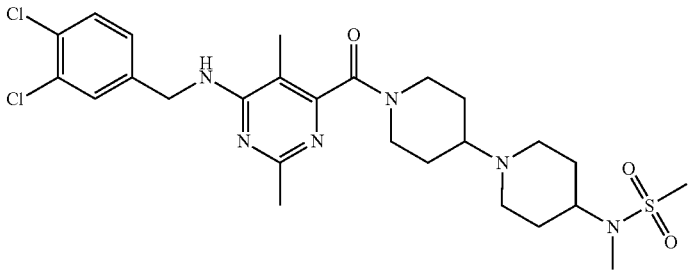
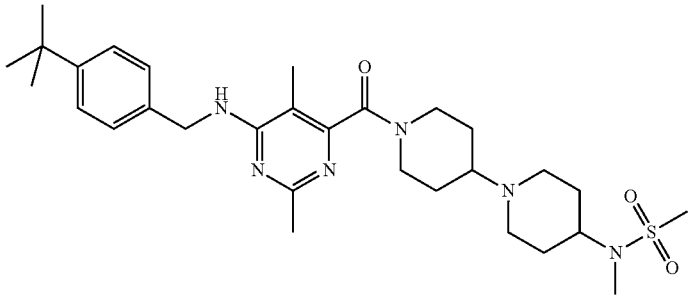
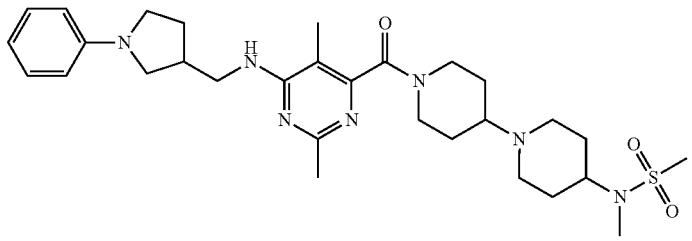
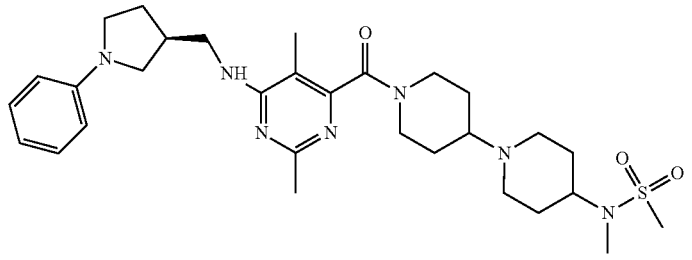
Ex #	STRUCTURE	Inter-me-diate	Amine	[M + H]+	HPLC R_t-(min)	Meth-od
81		251	3-chloro-4-tri-fluoro methyl-benzyl-amine	617	9.12	1E (Hydro)
82		251	3,4-di-chloro-benzyl-amine	583	8.83	1E (Hydro)
83		251	4-tert-butyl-benzyl-amine	571	9.73	1E (Hydro)
84		251	(1-phenyl-pyrrolidin-3-yl)-methan-amine	584	8.70-9.02	1E (Hydro)
85		251	9c	584	9.1	1E (Hydro)

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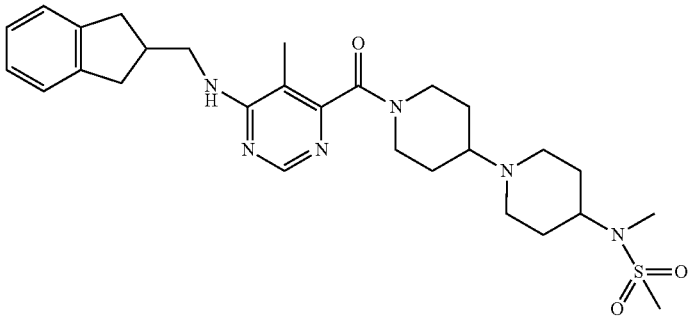
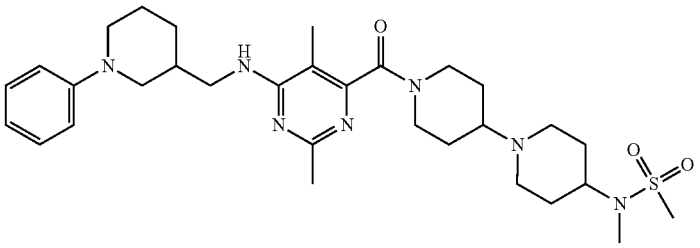
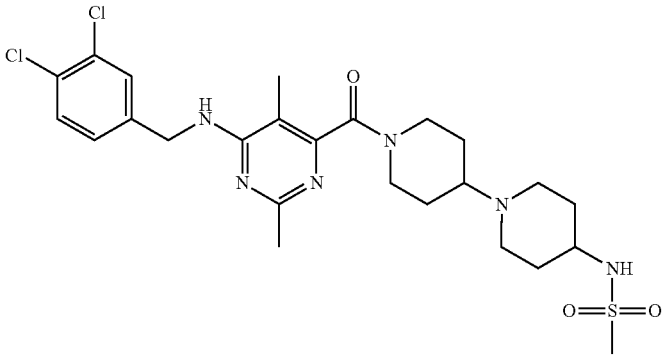
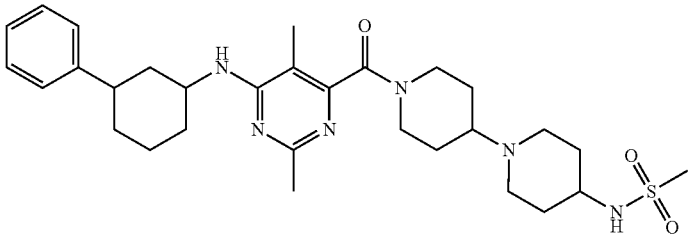
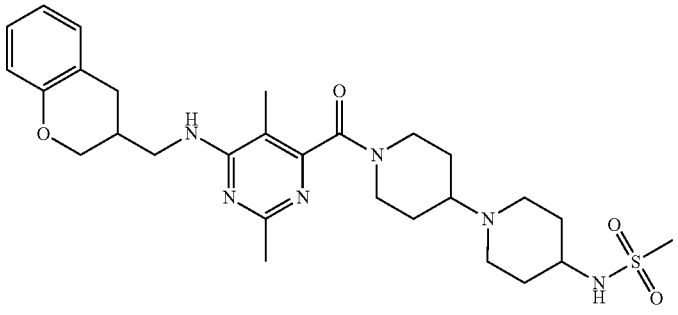
Ex #	STRUCTURE	Inter-me-diate	Amine	[M + H]+	HPLC R_t-(min)	Meth-od
86		25l	indan-2yl-methan-amine	555	8.80	1E (Hydro)
87		25l	9a	598	8.97	1E (Hydro)
88		25k	3,4-di-chloro-benzyl-amine	569	7.78	1E (Hydro)
89		25k	3-phenyl-cyclo-hexyl-amine	569	8.45	1E (Hydro)
90		25k	chroman-3-yl-methan amine	557	7.20	1E (Hydro)

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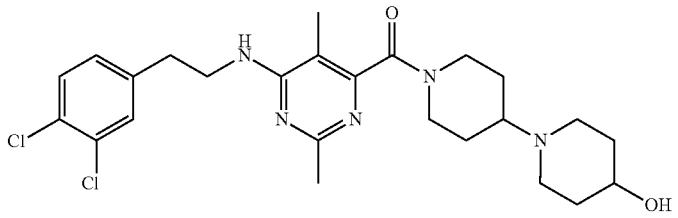
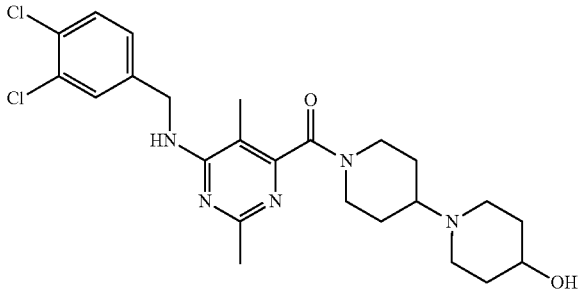
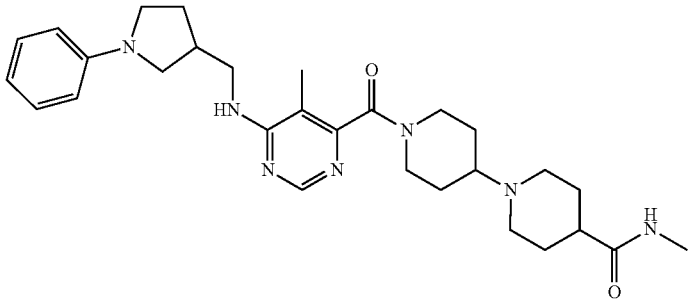
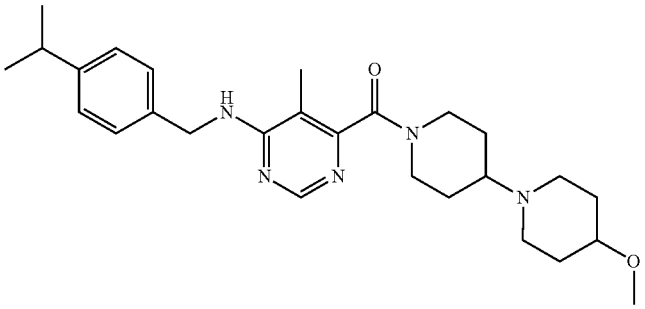
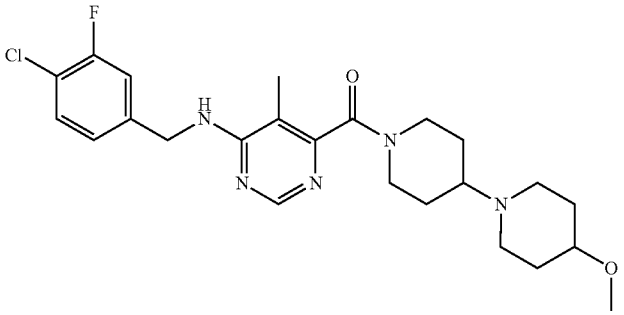
Ex #	STRUCTURE	Inter-me-diate	Amine	[M + H]+	HPLC R_t-(min)	Meth-od
91		25m	2-(3,4-dichloro-phenyl)-ethyl-amine	506	7.87	1E
92		25m	3,4-dichloro-benzyl-amine	492	7.62	1E
93		25d	(1-phenyl-pyrrolidin-3-yl)-methan-amine	520	7.70	1E (Hydro)
94		25g	4-iso-propyl-benzyl-amine	466	6.71	2F
95		25g	4-chloro-3-fluoro-benzyl-amine	476	9.18	1E (Hydro)

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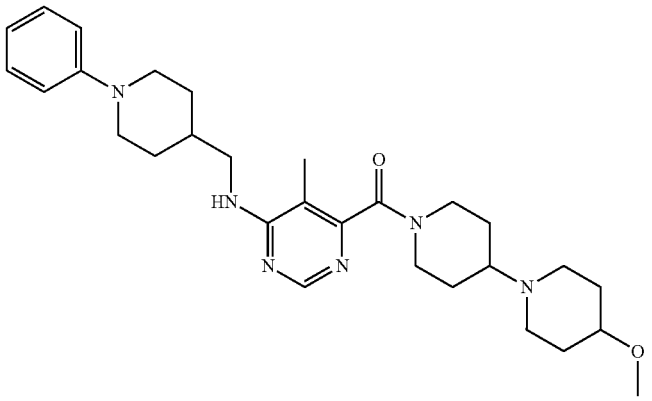
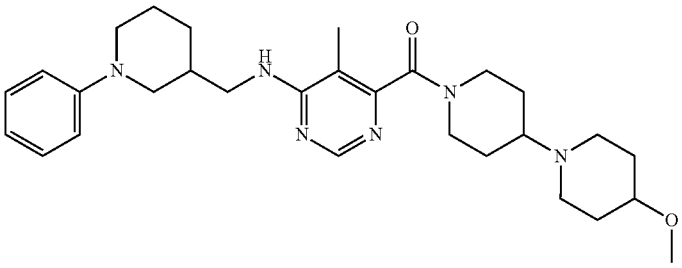
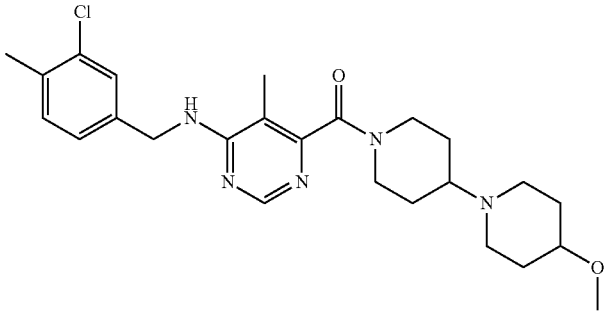
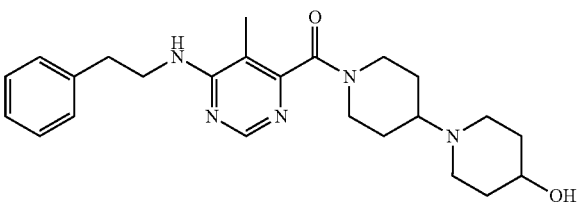
Ex #	STRUCTURE	Intermediate	Amine	[M + H]+	HPLC R_t.(min)	Method
96		25g	(1-phenyl-piperidin-4-yl)-methan-amine	507	9.55	1E (Hydro)
97		25g	9a	507	1.22	2F
98		25g	3-chloro-4-methyl-benzyl-amine	472	9.62	1E (Hydro)

Example 99

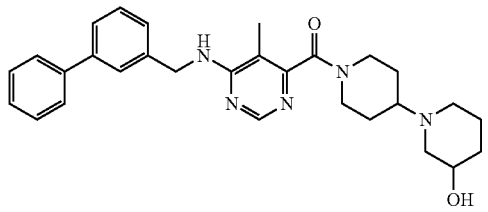
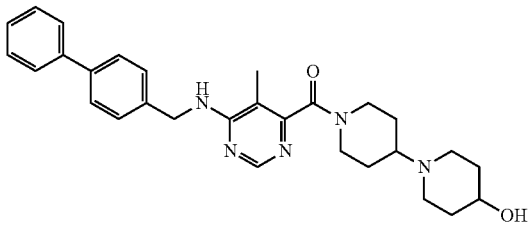
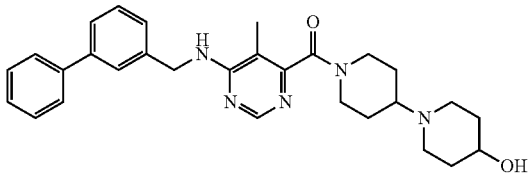
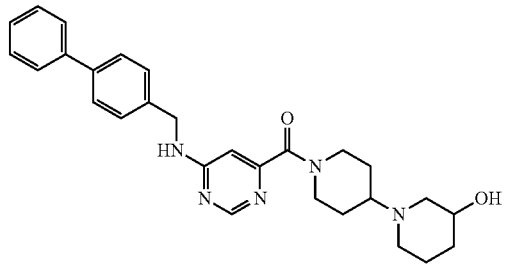


Intermediate 2a (200 mg, 1.047 mmol) was dissolved in 30 ml of dichloromethane. [1,4']Bipiperidinyl-4-ol (192 mg, 1.047 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under vacuum and the crude product was dissolved in 1 ml of DMSO. Phenethylamine (0.6 ml, 4.73 mmol) and N,N-diisopropyl-ethyl amine (0.013 ml, 0.075 mmol) were added and the reaction mixture was stirred at 80° C. overnight. The reaction mixture was concentrated under vacuum. The crude product was purified by reverse phase preparative HPLC. 331 mg (0.616 mmol) of the desired product were obtained.

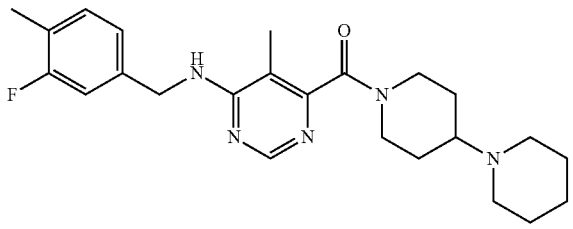
HPLC (Method C): R_t. (min)=1.34

$[M+H]^+$=424

The following examples were synthesized in analogy to the preparation of Example 99.

Ex #	STRUCTURE	Intermediate	Inter-mediate	Amine	[M + H]+	HPLC R_t (min)	Method
100		2a	[1,4']-Bipiper-idinyl-3-ol	Biphenyl-3-yl-methan-amine	486	1.53	2C
101		2a	[1,4']Bi-piperidinyl-4-ol	Biphenyl-4-yl-methan-amine	486	1.51	2C
102		2a	[1,4']Bi-piperidinyl-4-ol	Biphenyl-3-yl-methan-amine	486	1.52	2C
103		6-chloro-pyrimidine-4-carbonyl chloride	[1,4']-Bipiperidin-in-yl-3-ol	Biphenyl-4-yl-methan-amine	472	1.59	2C

Example 104

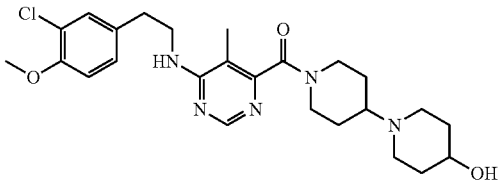
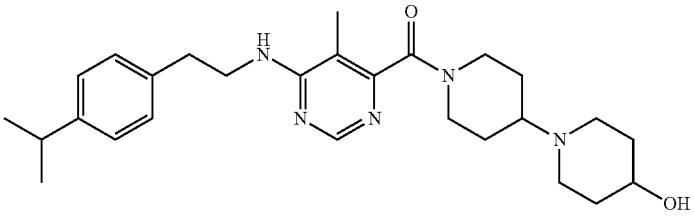
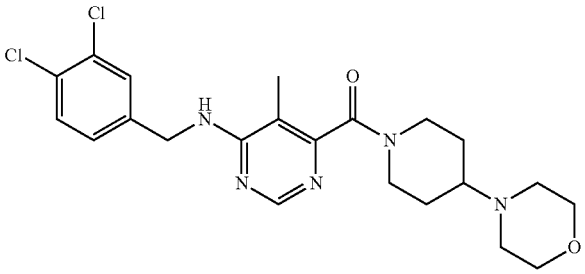
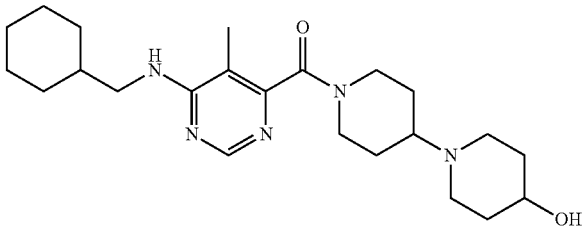
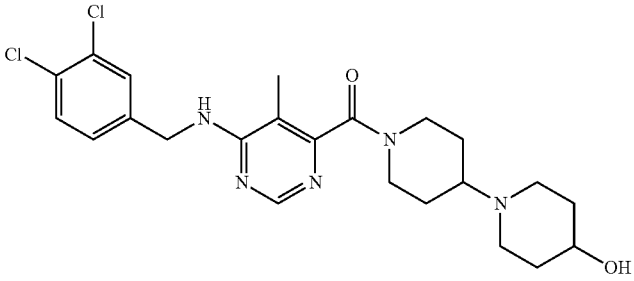
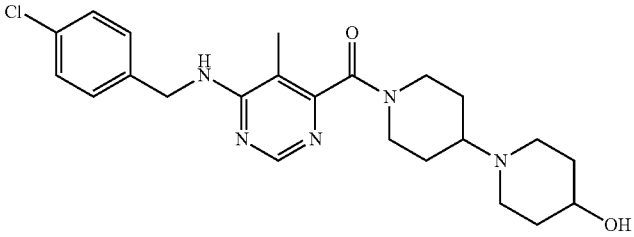


Intermediate 25i (17 mg, 0.05 mmol), 3-fluoro-4-methyl-benzylamine (10 mg, 0.075 mmol) and diisopropyl-ethyl amine (0.013 ml, 0.075 mmol) in 1 ml of dry DMSO were stirred at 80° C. overnight. The reaction mixture was concentrated under vacuum. The crude product was purified by reverse phase preparative HPLC. 20 mg (0.047 mmol) of the desired product were obtained.

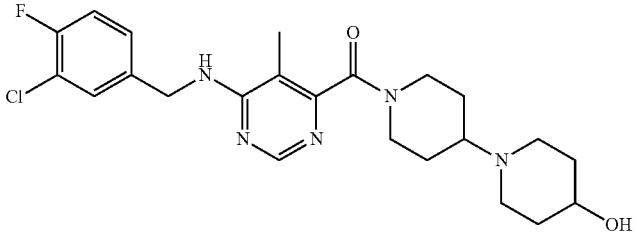
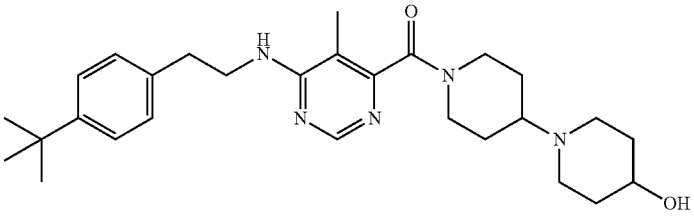
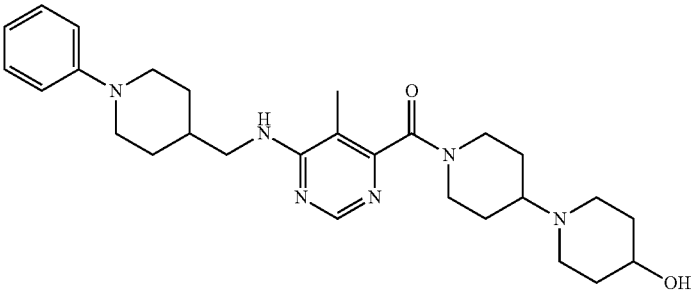
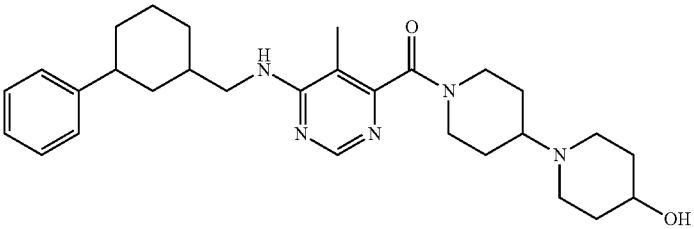
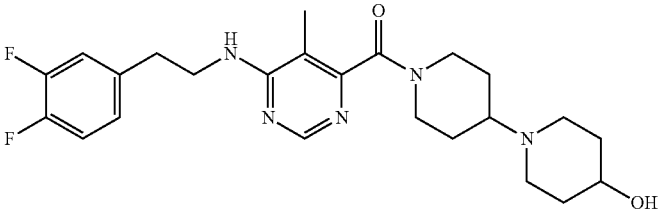
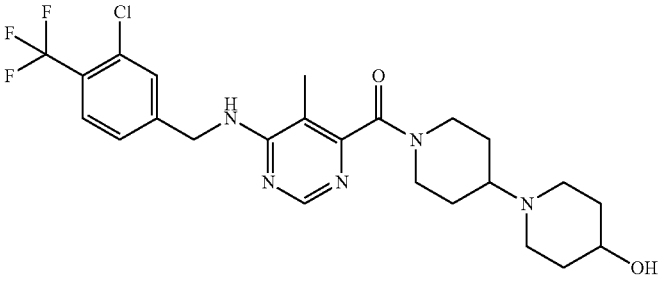
HPLC (Method C): R_t. (min)=1.45

$[M+H]^+$=426

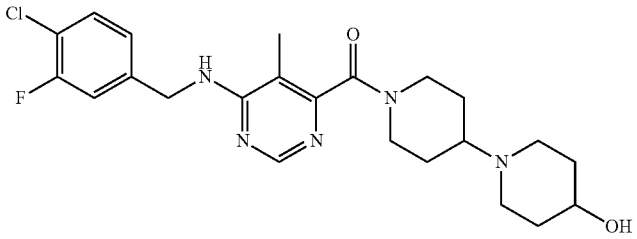
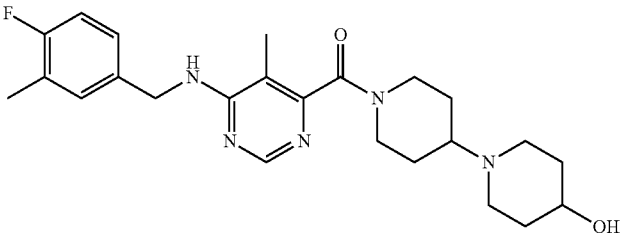
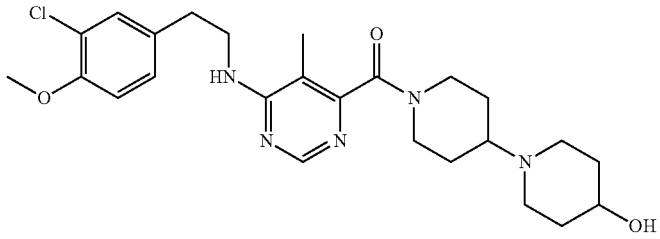
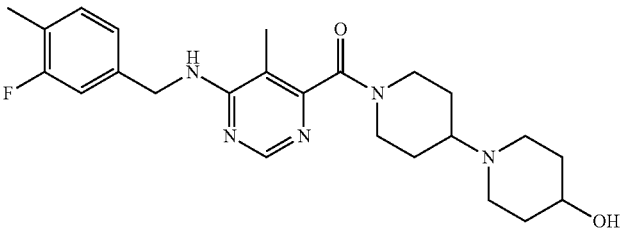
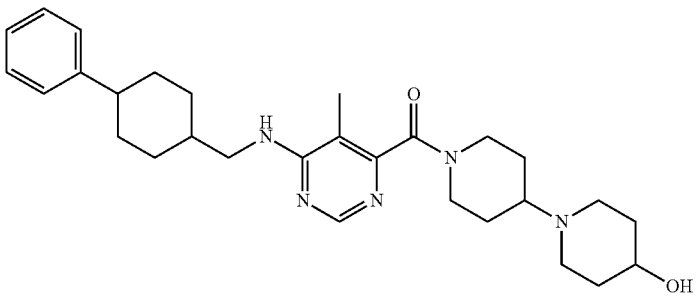
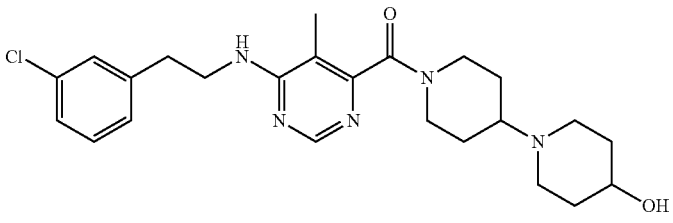
The following examples were synthesized in analogy to the preparation of Example 104.

Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R_t (min)	Method
105		25f	2-(3-chloro-4-methoxy-phenyl)-ethyl-amine	488	1.43	2C
106		25f	2-(4-isopropyl-phenyl)-ethylamine	466	2.88	2B
107		25h	3,4-dichloro-benzyl-amine	464	5.6	1A
108		25f	Cyclohexyl-methan-amine	416	2.67	2B
109		25f	3,4-dichloro-benzyl-amine	478	2.81	2B
110		25f	4-chloro-benzyl-amine	444	1.6	2A

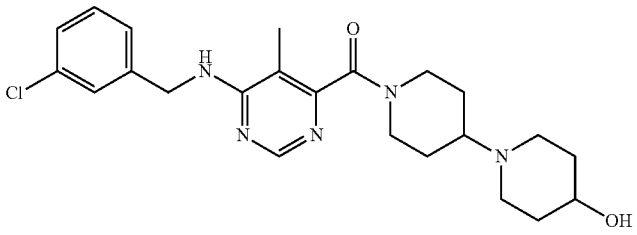
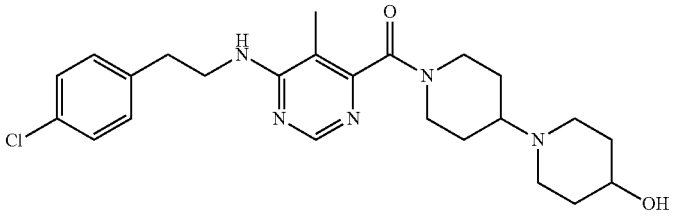
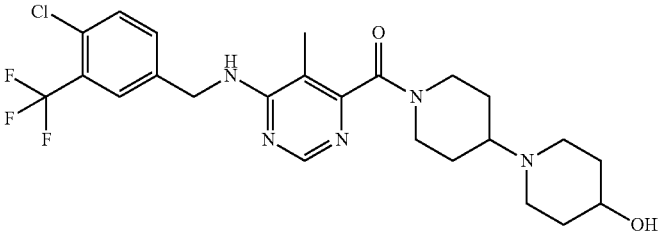
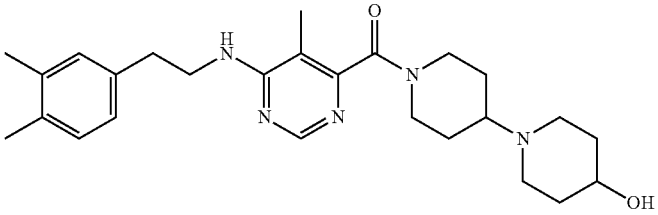
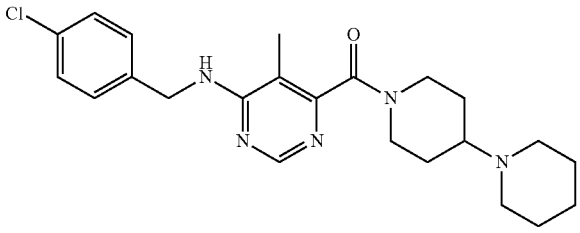
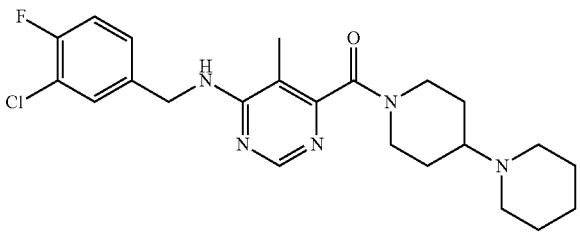
-continued

Ex #	STRUCTURE	Intermediate	Amine	$[M + H]^+$	HPLC R_t (min)	Method
111		25f	3-chloro-4-fluoro-benzyl-amine	462	1.63	2A
112		25f	2-(4-tert-butyl-phenyl)-ethylamine	480	1.8	2A
113		25f	(1-phenyl-piperidin-4-yl)methan-amine	493	1.32	2A
114		25f	7a	492	7.42	2F
115		25f	2-(3,4-difluoro-phenyl)-ethylamine	460	1.61	2A
116		25f	3-chloro-4-tri-fluoro-methyl-benzyl-amine	512	1.74	2A

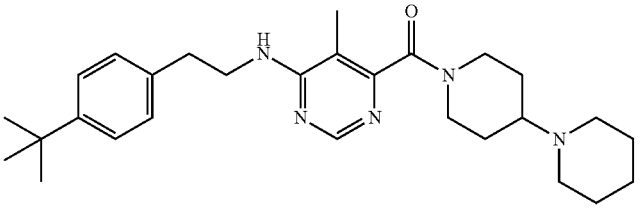
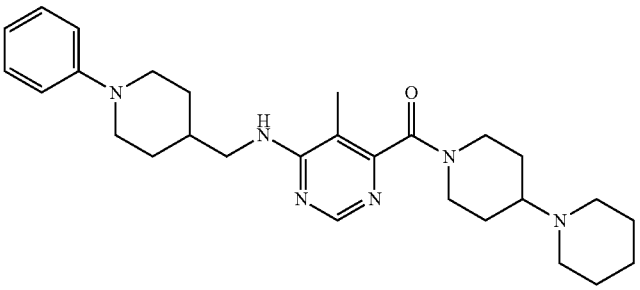
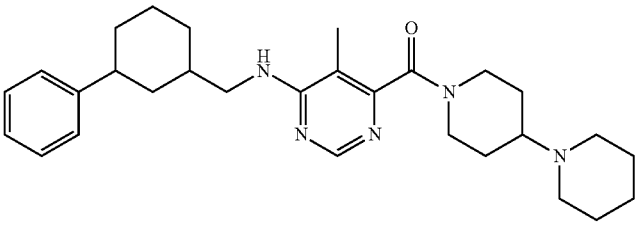
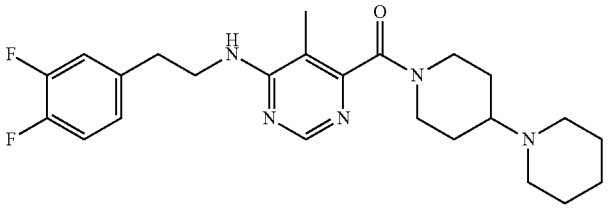
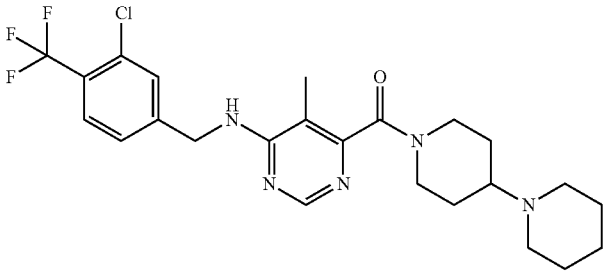
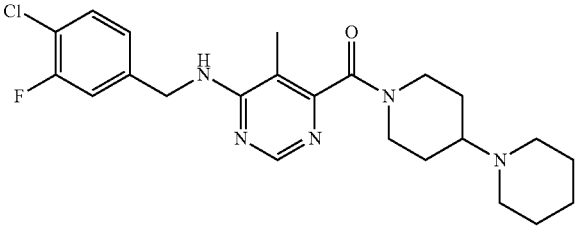
-continued

Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R_t (min)	Method
117		25f	4-chloro-3-fluoro-benzyl-amine	462	1.64	2A
118		25f	4-fluoro-3-methyl-benzyl-amine	442	1.61	2A
119		25f	2-(3-chloro-4-methoxy-phenyl)-ethyl-amine	488	1.63	2A
120		25f	3-fluoro-4-methyl-benzyl-amine	442	1.61	2A
121		25f	(4-phenylcyclo-hexyl)-methan-amine	492	1.78	2A
122		25f	2-(3-chloro-phenyl)-ethylamine	458	1.63	2A

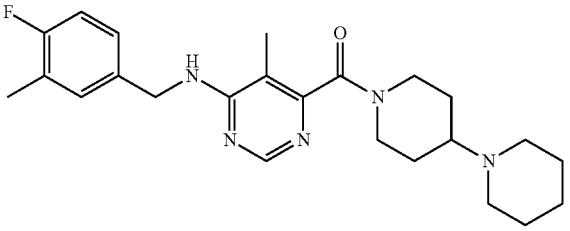
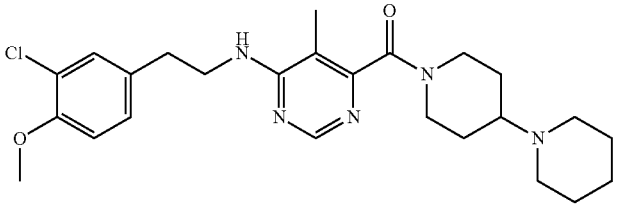
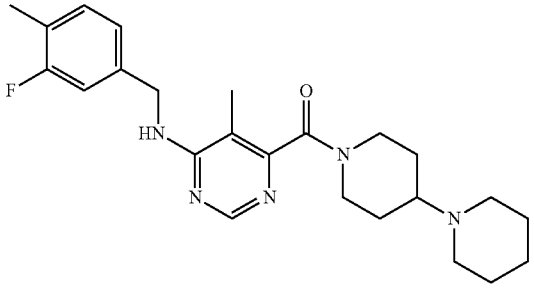
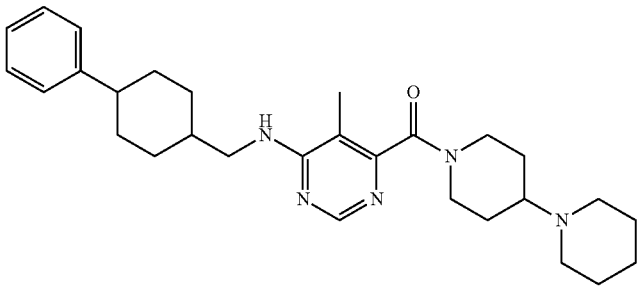
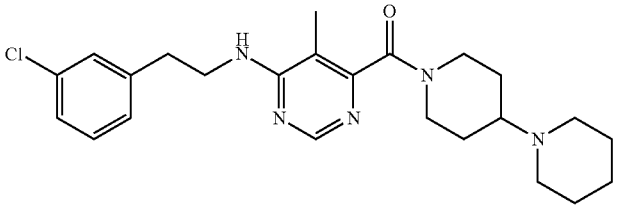
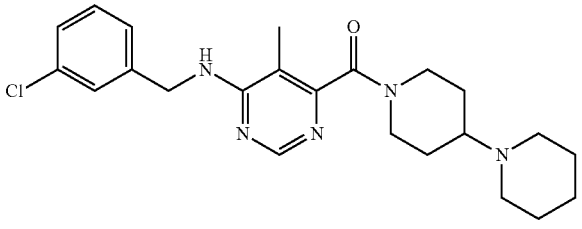
-continued

Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R_t (min)	Method
123		25f	3-chloro-benzyl-amine	444	1.6	2A
124		25f	2-(4-chloro-phenyl)-ethylamine	458	1.65	2A
125		25f	4-chloro-3-trifluoro-methyl-benzyl-amine	512	1.74	2A
126		25f	2-(3,4-dimethyl-phenyl)-ethylamine	452	1.68	2A
127		25i	4-chloro-benzyl-amine	428	1.65	2A
128		25i	3-chloro-4-fluoro-benzyl-amine	446	1.67	2A

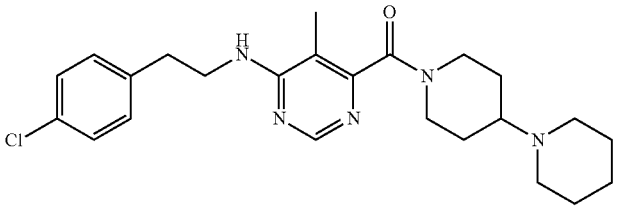
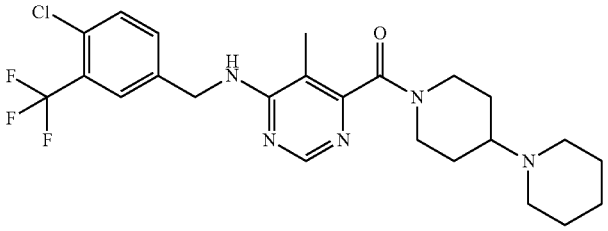
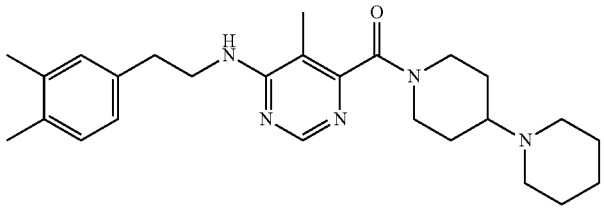
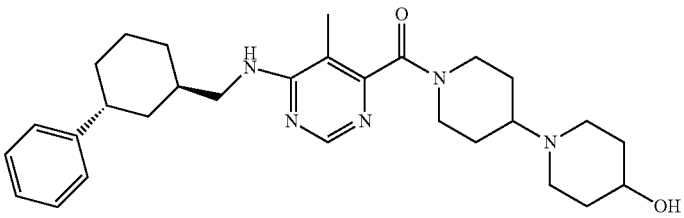
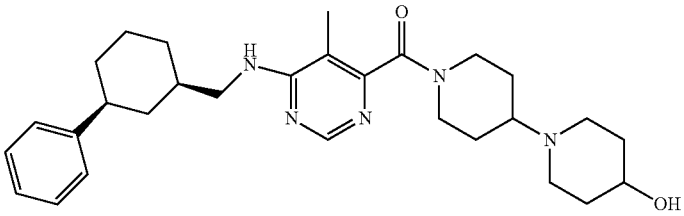
-continued

Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R_t (min)	Method
129		25i	2-(4-tert-butyl-phenyl)-ethylamine	464	1.84	2A
130		25i	(1-phenyl-piperidin-4-yl)-methan-amine	477	1.37	2A
131		25i	7a	476	1.84	2A
132		25i	2-(3,4-difluoro-phenyl)-ethylamine	444	1.66	2A
133		25i	3-chloro-4-trifluoro-methyl-benzyl-amine	496	1.79	2A
134		25i	4-chloro-3-fluoro-benzyl-amine	446	1.67	2A

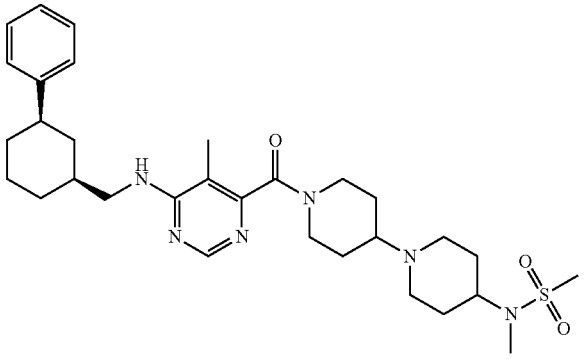
-continued

Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R_t (min)	Method
135		25i	4-fluoro-3-methyl-benzyl-amine	426	1.65	2A
136		25i	2-(3-chloro-4-methoxy-phenyl)-ethylamine	472	1.66	2A
137		25i	3-fluoro-4-methyl-benzyl-amine	426	1.65	2A
138		25i	(4-phenylcyclo-hexyl)-methan-amine	476	1.84	2A
139		25i	2-(3-chloro-phenyl)-ethylamine	442	1.68	2A
140		25i	3-chloro-benzyl-amine	428	1.64	2A

-continued

Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R_t (min)	Method
141		25i	2-(4-chloro-phenyl)-ethylamine	442	1.69	2A
142		25i	4-chloro-3-trifluoro-methyl-benzyl-amine	496	1.79	2A
143		25i	2-(3,4-dimethyl-phenyl)-ethylamine	436	1.72	2A
144		25f	7a	492	7.7	2H (iso-cratic)
145		25f	7a	492	10.2	2H (iso-cratic)

Example 146

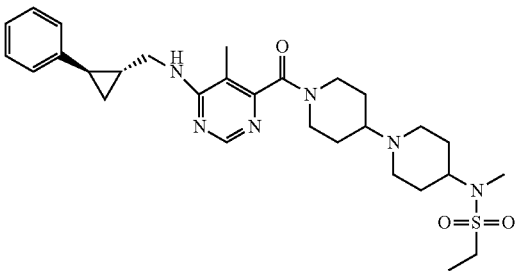
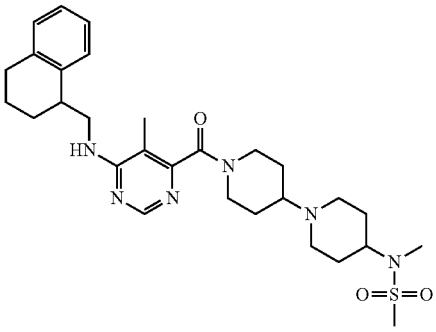
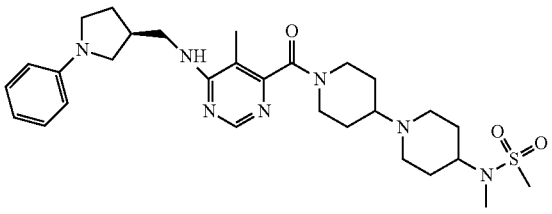


Intermediate 25b (80 mg, 0.18 mmol), Intermediate 7c (40 mg, 0.21 mmol) and N,N-diisopropyl-ethyl amine (0.046 ml, 0.26 mmol) in 0.2 ml of dry 1,4-dioxane were mixed in a microwave vial and reacted in the following conditions: Power 100, Ramp 5 min, Hold 2 h, Temperature 150° C., Pression 150° C., Stirring. The reaction mixture was concentrated under vacuum and diluted with dichloromethane. The organic phase was washed with an aqueous saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by reverse phase preparative HPLC. 36 mg (0.06 mmol) of the desired product were obtained.

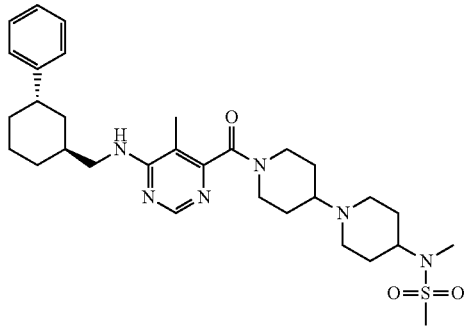
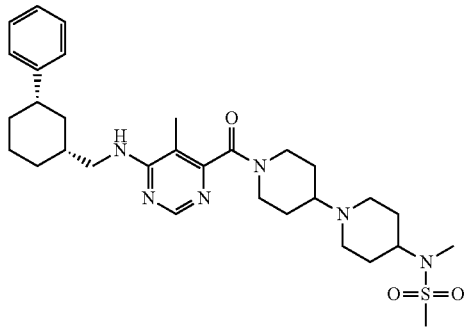
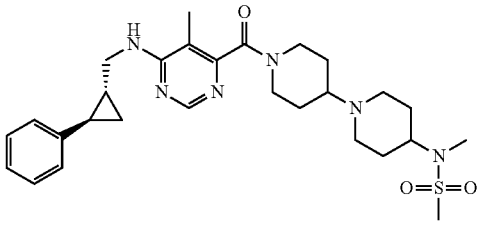
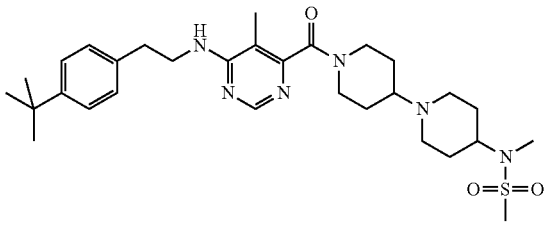
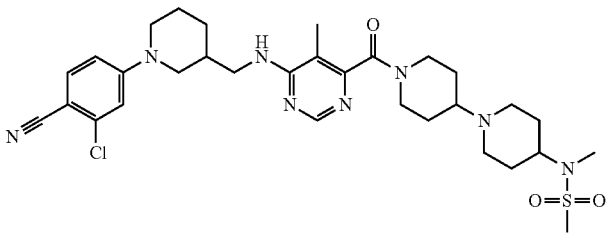
HPLC (Method 1E Hydro): R_t. (min)=9.52

$[M+H]^+$=583

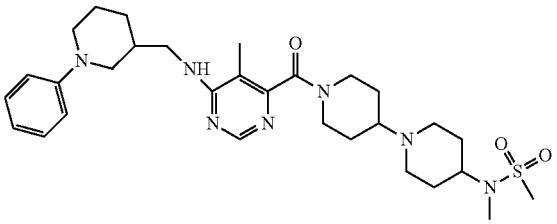
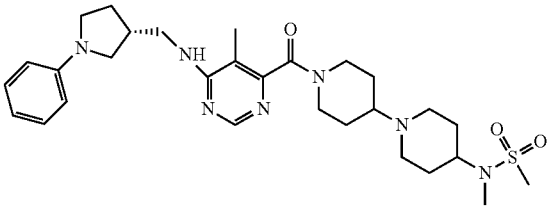
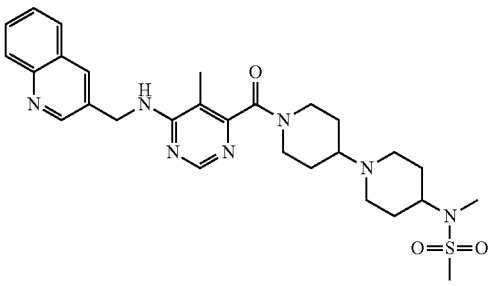
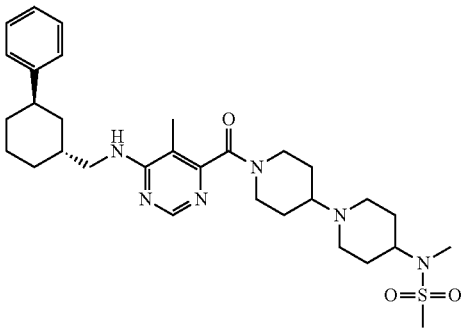
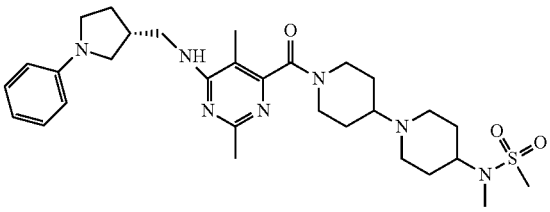
The following examples were synthesized in analogy to the preparation of Example 146

Ex #	STRUCTURE	Intermediate	Amine	$[M + H]^+$	HPLC R_t. (min)	Method
147		25c	(trans-2-phenyl-cyclo-propyl)-methan-amine	555	8.48	1E (Hydro)
148		25b	(1,2,3,4-tetrahydro-naphthalen-1-yl)-methan-amine	555	8.62	1E (Hydro)
149		25b	9c	570	8.7	1E (Hydro)

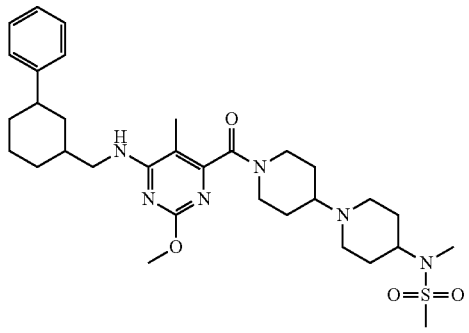
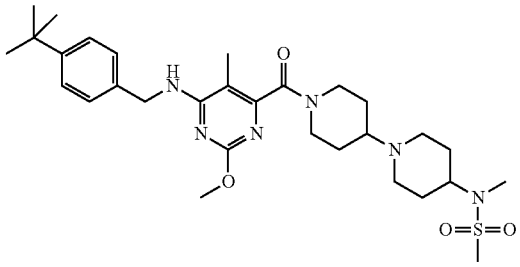
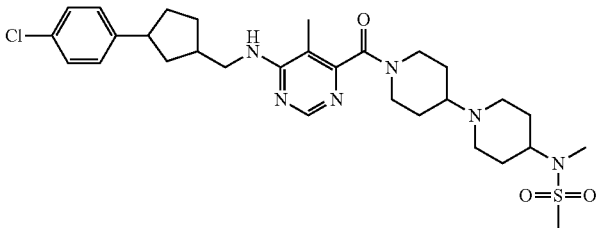
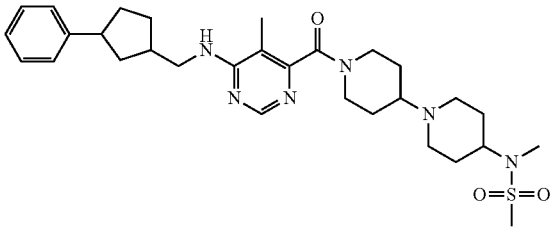
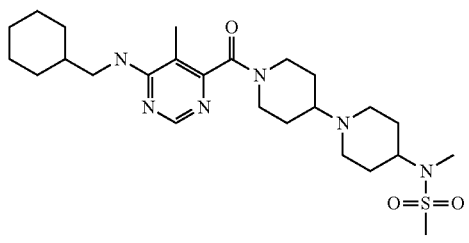
-continued

Ex #	STRUCTURE	Intermediate	Amine	$[M + H]^+$	HPLC R_t (min)	Method
150		25b	7d	583	9.12	1E (Hydro)
151		25b	7e	583	9.22	1E (Hydro)
152		25b	(trans-2-phenyl-cyclo-propyl)-methan-amine	541	8.03	1E (Hydro)
153		25b	2-(4-tert-butyl-phenyl)-ethyl-amine	571	9.42	1E (Hydro)
154		25b	11	643	8.65	1E (Hydro)

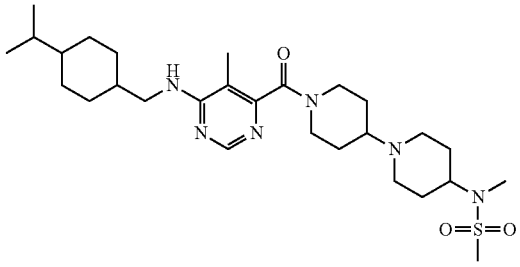
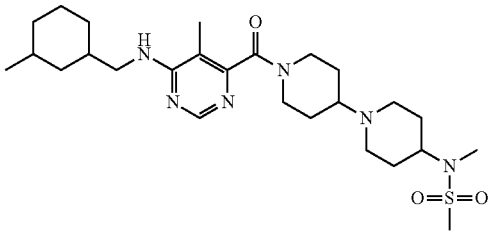
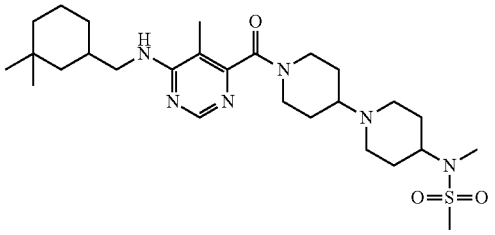
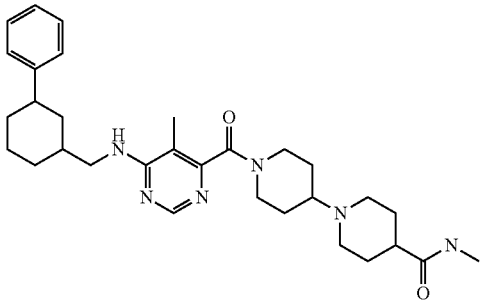
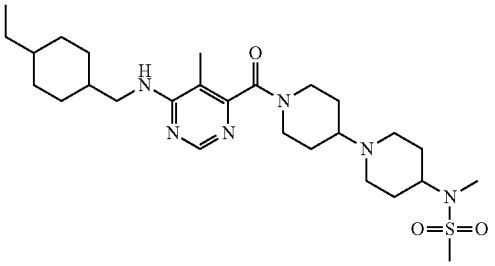
-continued

Ex #	STRUCTURE	Intermediate	Amine	$[M + H]^+$	HPLC R_t (min)	Method
155		25b	9a	584	8.52	1E (Hydro)
156		25b	9b	570	8.48	1E (Hydro)
157		25b	Quinolin-3-ylmethan-amine	552	1.28	2F
158		25b	7b	583	9.48	1E (Hydro)
159		25l	9b	584	8.85	1E (Hydro)

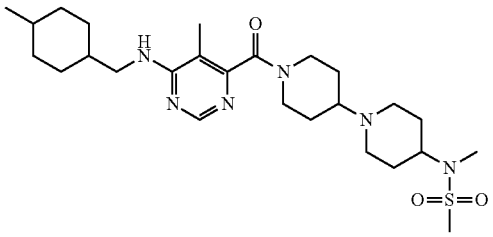
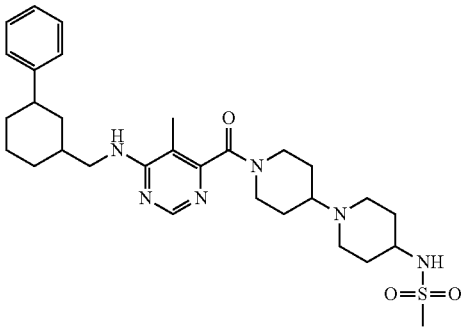
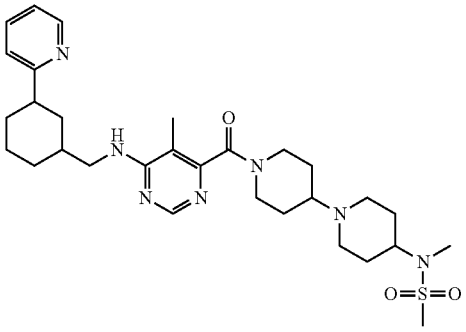
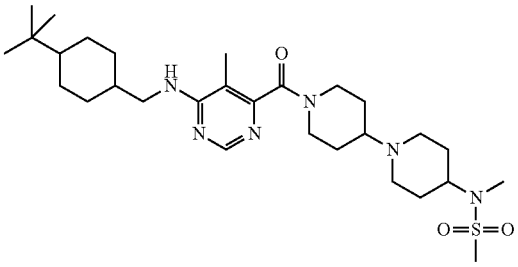
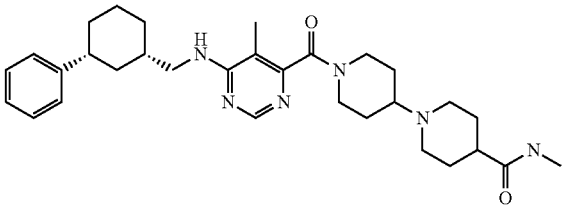
-continued

Ex #	STRUCTURE	Intermediate	Amine	[M + H]+	HPLC R_t (min)	Method
159a		25n	7a	613	2.21	2Ca
159b		25n	4-tert-butyl-benzyl-amine	587	1.89	2Ca
159c		25b	7m	603	9.88	1E (Hydro)
159d		25b	7l	569	9.62	1E (Hydro)
159e		25b	C-Cyclohexyl-methyl-amine	507	8.37	1E (Hydro)

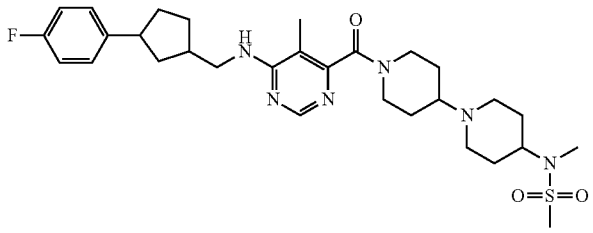
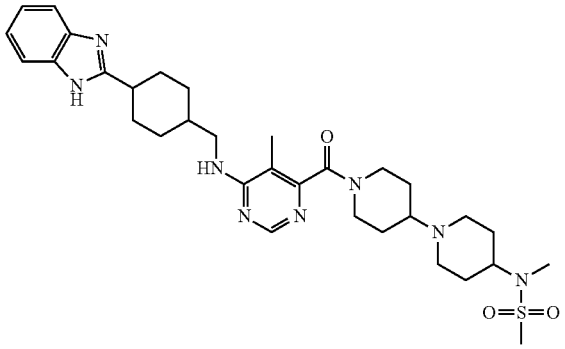
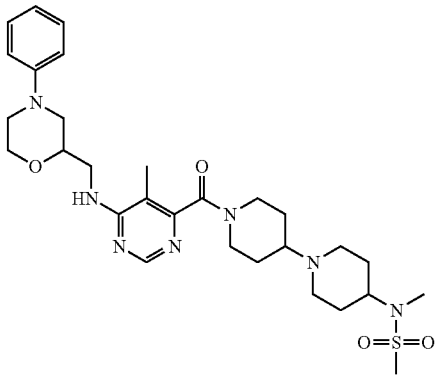
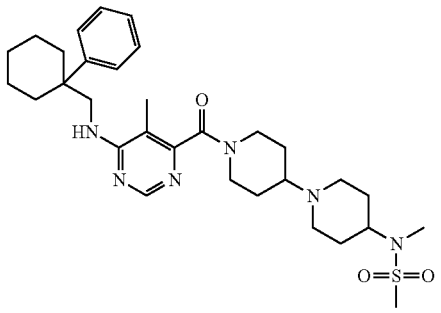
-continued

Ex #	STRUCTURE	Intermediate	Amine	$[M + H]^+$	HPLC R_t (min)	Method
159f		25b	C-(4-isopropyl-cyclo-hexyl)-methyl-amine	549	10.12	1E (Hydro)
159g		25b	C-(3-methyl-cyclo-hexyl)-methyl-amine	521	9.25	1E (Hydro)
159h		25b	C-(3,3-dimethyl-cyclo-hexyl)-methyl-amine	535	9.68	1E (Hydro)
159i		25d	7a	533	9.53	1E (Hydro)
159k		25b	C-(4-ethyl-cyclo-hexyl)-methyl-amine	535	9.98	1E (Hydro)

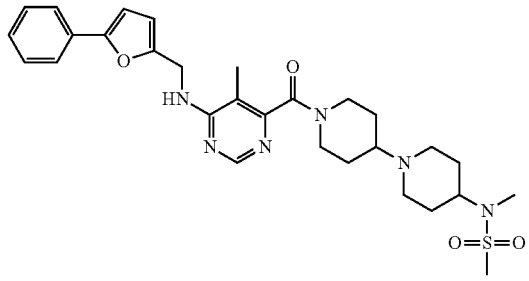
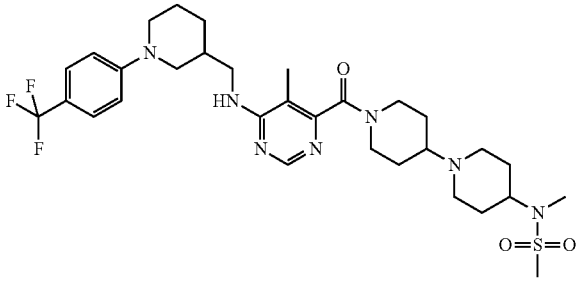
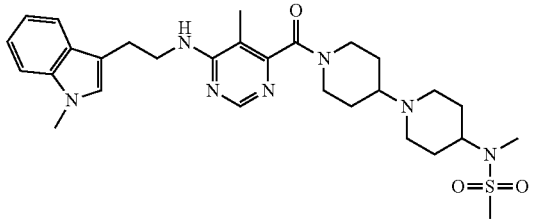
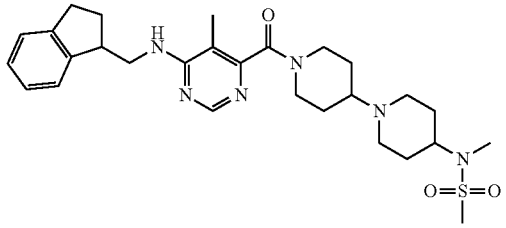
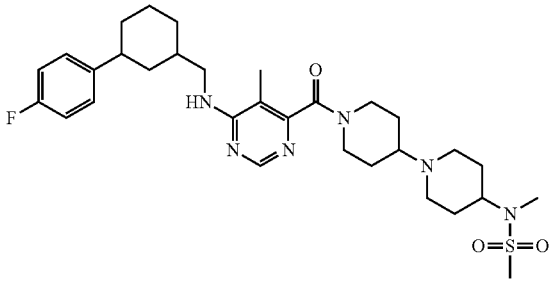
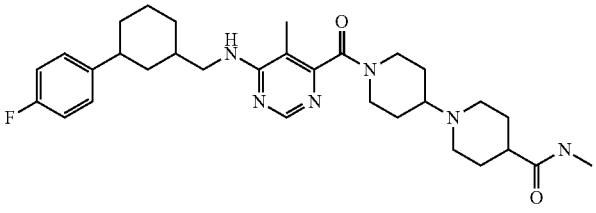
-continued

Ex #	STRUCTURE	Intermediate	Amine	$[M + H]^+$	HPLC R_t (min)	Method
159l		25b	C-(4-methyl-cyclo-hexyl)-methyl-amine	521	9.28	1E (Hydro)
159m		25a	7a	569	9.33	1E (Hydro)
159n		25b	C-(3-pyridin-2yl-cyclo-hexyl)-methyl-amine	584	7.90 8.05	1E (Hydro)
159o		25b	C-(4-tert-butyl-cyclo-hexyl)-methyl-amine	563	10.87	1E (Hydro)
159p		25d	7c	533	9.53	1E (Hydro)

-continued

Ex #	STRUCTURE	Intermediate	Amine	$[M + H]^+$	HPLC R_t (min)	Method
159q		25b	7n	587	9.37	1E (Hydro)
159r		25b	C-[4-(1H-Benzo-imidazol-2-yl)-cyclo-hexyl]-methyl-amine	623	7.17	1E (Hydro)
159s		25b	C-[(4-phenyl-morpholin-2-yl)-methyl-amine	586	7.73	1E (Hydro)
159t		25b	C-(1-pheny-cyclo-hexyl)-methyl-amine	583	9.5	1E (Hydro)

-continued

Ex #	STRUCTURE	Intermediate	Amine	[M + H]+	HPLC R_t (min)	Method
159u		25b	C-(5-pheny-furan-2yl)-methyl-amine	567	8.93	1E (Hydro)
159w		25b	9d	652	9.57	1E (Hydro)
159y		25b	2-(1-methyl-1H-indol-3yl)-ethyl-amine	568	8.2	1E (Hydro)
159x		25b	C-Indan-1-yl-methyl-amine	541	8.27	1E (Hydro)
159z		25b	7g	601	9.8	1E (Hydro)
159aa		25d	7g	551	9.47	1E (Hydro)

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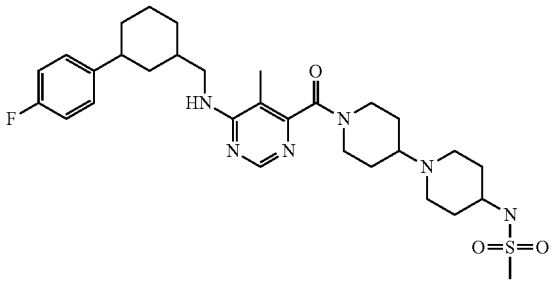
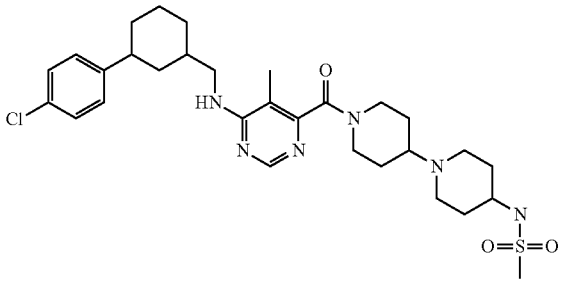
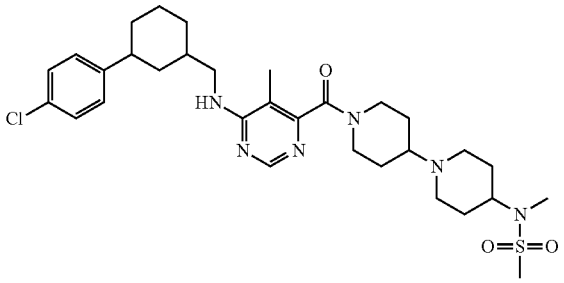
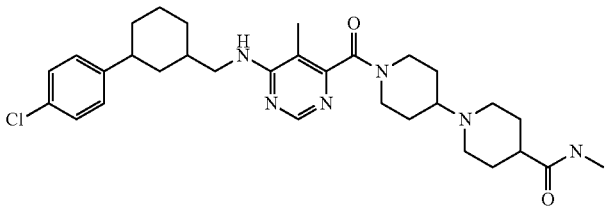
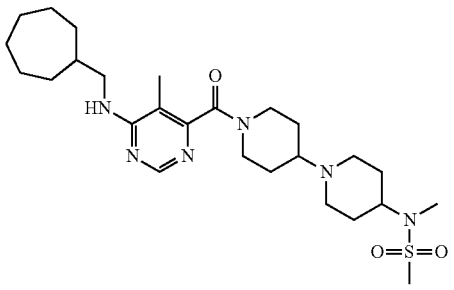
Ex #	STRUCTURE	Intermediate	Amine	$[M + H]^+$	HPLC R_t (min)	Method
159ba		25a	7g	587	9.32	1E (Hydro)
159ca		25a	7f	603	9.95	1E (Hydro)
159da		25b	7f	617	10.5	1E (Hydro)
159ea		25d	7f	567	7.4	2F
159fa		25b	C-cyclo-heptyl-methyl-amine	521	8.88	1E (Hydro)

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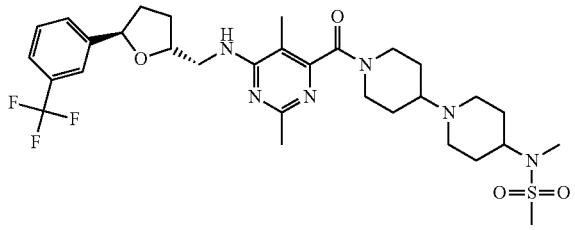
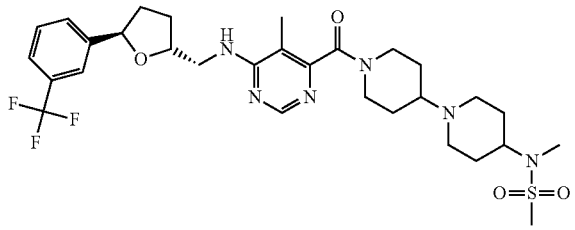
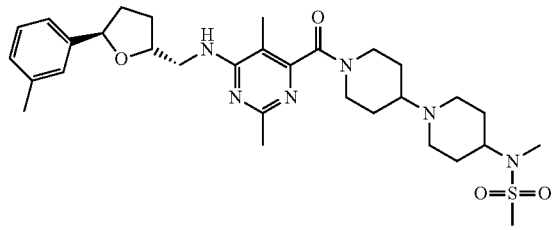
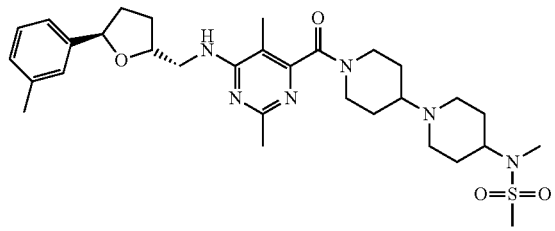
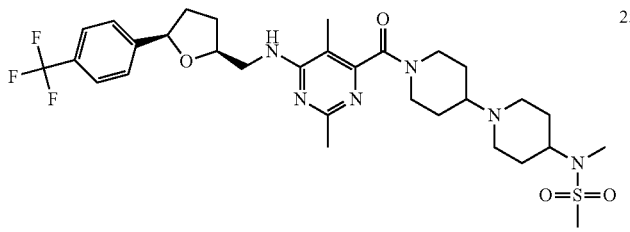
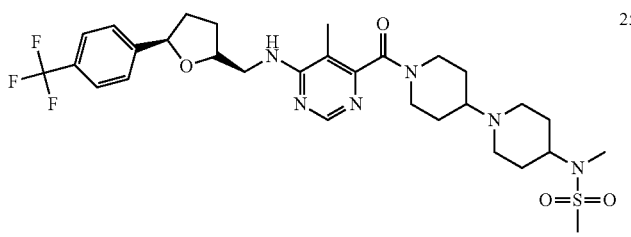
Ex #	STRUCTURE	Intermediate	Amine	$[M + H]^+$	HPLC R_t (min)	Method
159ga		25l	54a	653	5.38	2M
159ha		25b	54a	639	5.94	2M
159ia		25b	54b	585	5.42	2M
159ja		25l	54b	599	4.76	2M
159ka		25l	55g	653	9.37	1E (Hydro)
159la		25b	55g	639	9.02	1E (Hydro)

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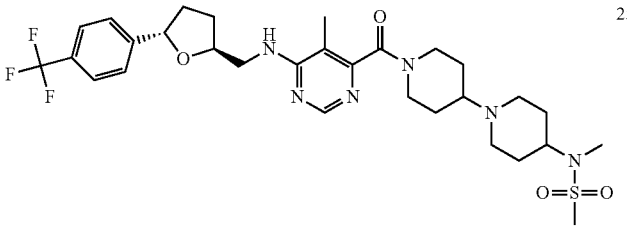
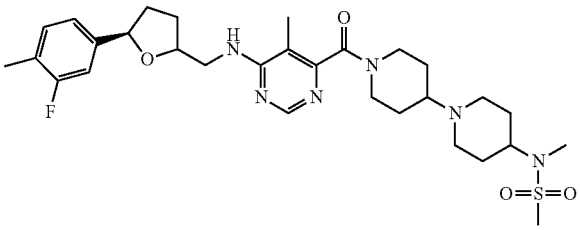
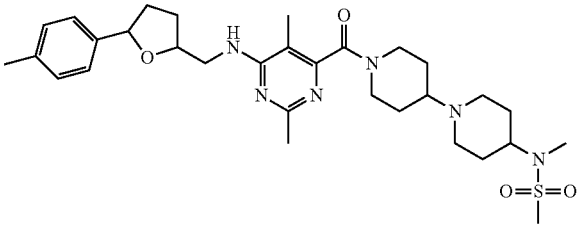
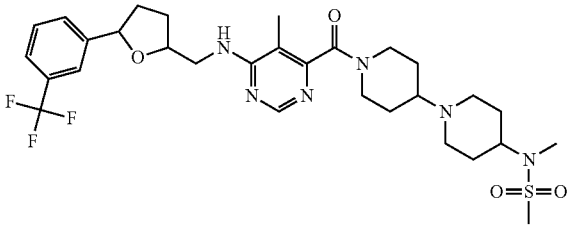
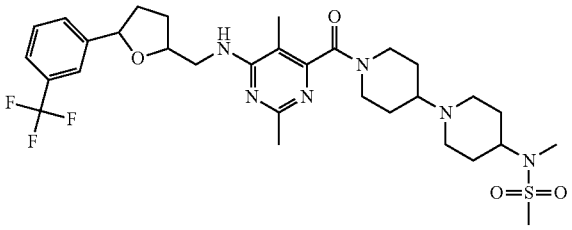
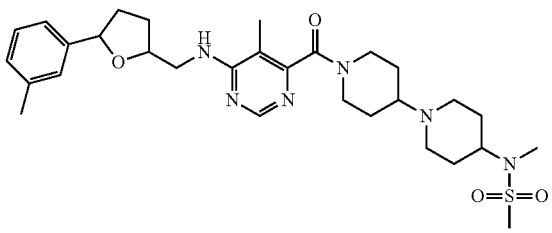
Ex #	STRUCTURE	Intermediate	Amine	$[M + H]^+$	HPLC R_t (min)	Method
159ma		25b	54g	639	9.07	1E (Hydro)
159na		25b	53e	603	8.6	1E (Hydro)
159oa		25l	53c	599	9.01	1E (Hydro)
159pa		25b	53a	639	8.38	1E (Hydro)
159qa		25l	53a	653	8.85	1E (Hydro)
159ra		25b	53b	585	7.86	1E (Hydro)

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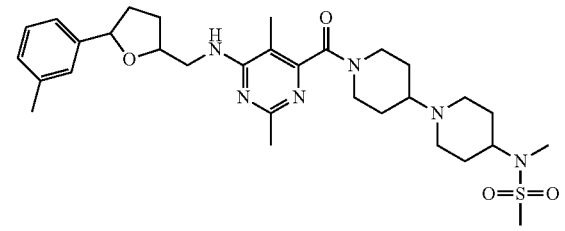
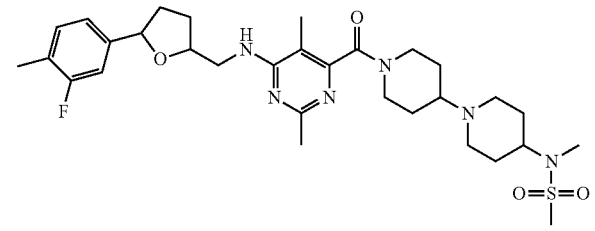
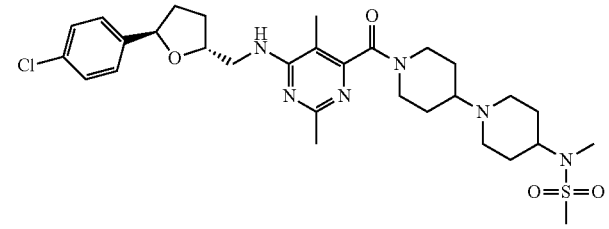
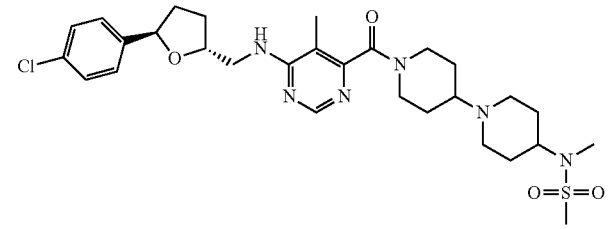
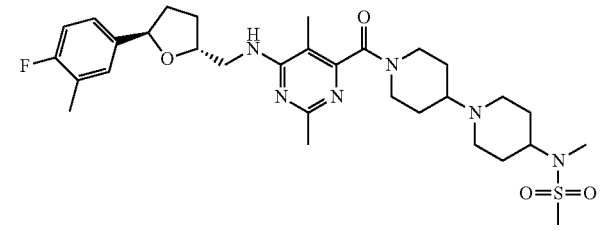
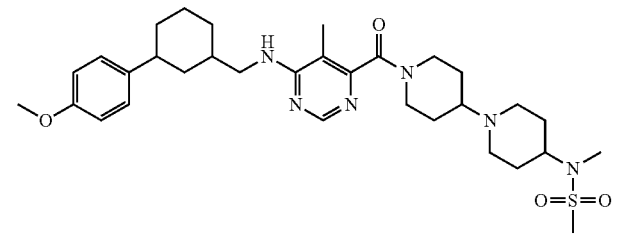
Ex #	STRUCTURE	Intermediate	Amine	$[M + H]^+$	HPLC R_t (min)	Method
159sa		25l	53b	599	8.36	1E (Hydro)
159ta		25l	53e	617	9.03	1E (Hydro)
159ua		25l	54f	619	8.63	1E (Hydro)
159wa		25b	54f	605	8.10	1E (Hydro)
159ya		25l	54d	617	5.08	2M
159xa		25b	7h	613	9.95	1E (Hydro)

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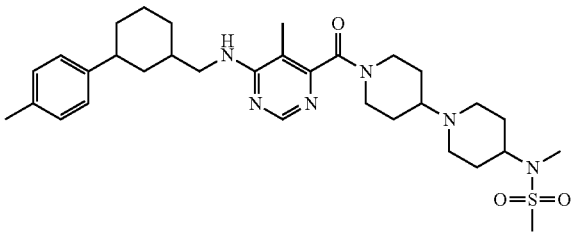
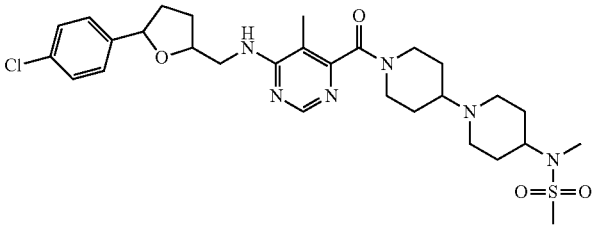
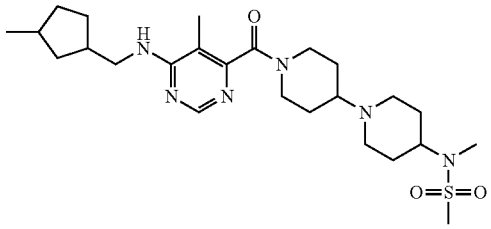
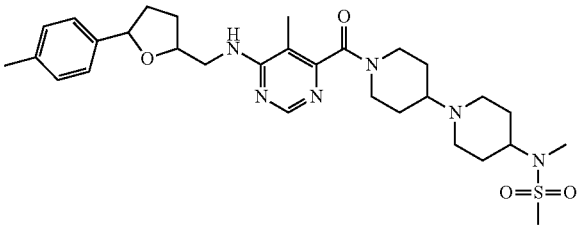
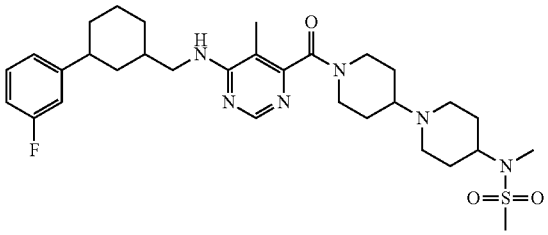
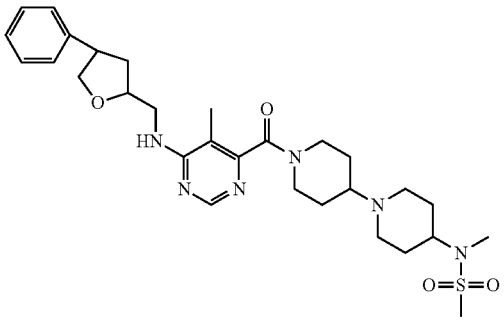
Ex #	STRUCTURE	Intermediate	Amine	$[M + H]^+$	HPLC R_t (min)	Method
159za		25b	7i	597	10.52	1E (Hydro)
159ab		25b	53f	605	9.0	1E (Hydro)
159bb		25b	C-(3-methyl-cyclo-pentyl)-methyl-amine	507	8.53	1E (Hydro)
159cb		25b	53c	585	8.77	1E (Hydro)
159db		25b	7j	601	10	1E (Hydro)
159eb		25b	53h	571	7.93	1E (Hydro)

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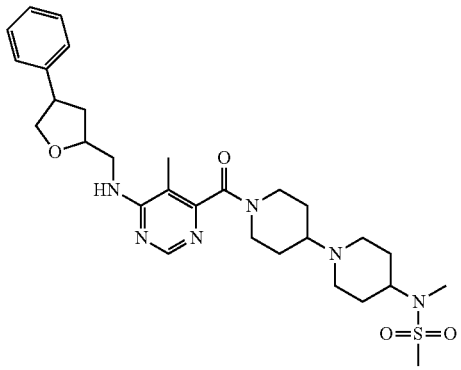
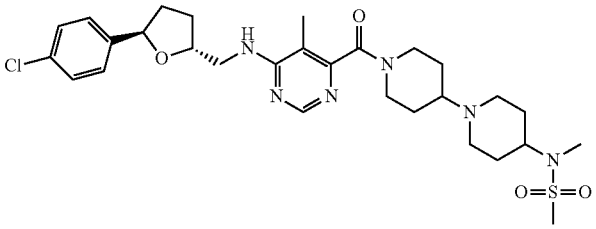
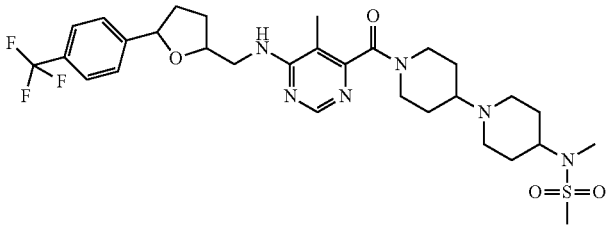
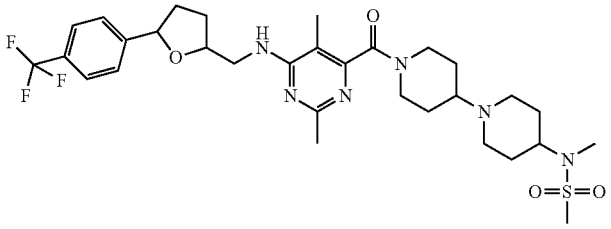
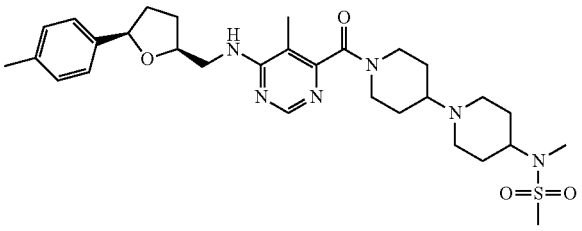
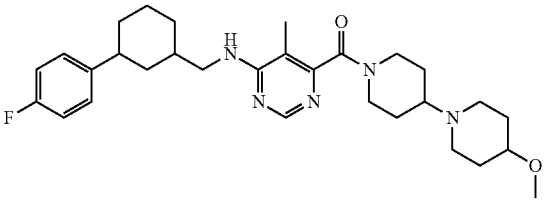
Ex #	STRUCTURE	Intermediate	Amine	$[M + H]^+$	HPLC R_t (min)	Method
159fb		25b	C-(5-phenyl-tetrahydro-furan-3yl)-methyl-amine	571	7.83	1E (Hydro)
159gb		25b	54c	585	8.36	1E (Hydro)
159hb		25b	53g	639	8.94	1E (Hydro)
159ib		25l	53g	653	9.27	1E (Hydro)
159jb		25b	55c	585	8.38	1E (Hydro)
159kb		25g	7g	524	2.87	1Fa

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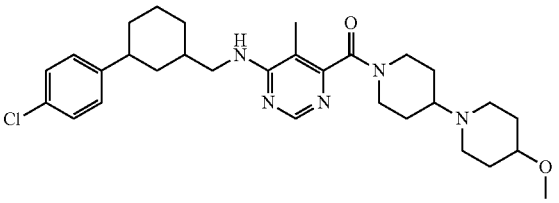
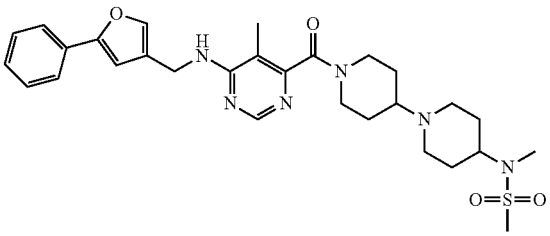
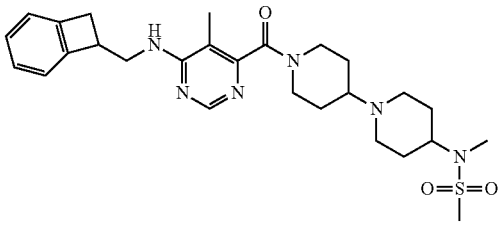
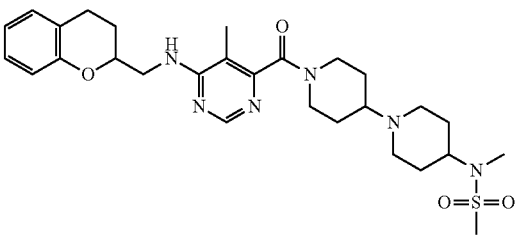
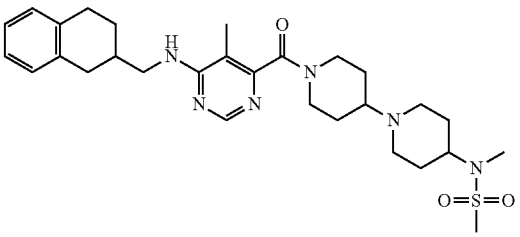
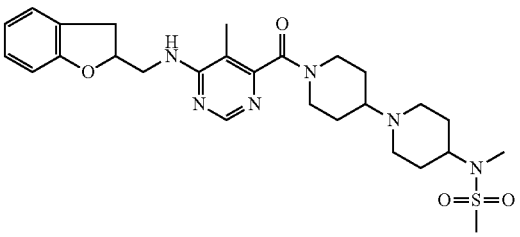
Ex #	STRUCTURE	Intermediate	Amine	$[M + H]^+$	HPLC R_t (min)	Method
159lb		25g	7f	540	3.02	1Fa
159mb		25b	7r	567	8.85	1E (Hydro)
159nb		25b	C-Bicyclo[4.2.0]octa-1(6),2,4-trien-7-yl-methyl-amine	527	7.53	1E (Hydro)
159ob		25b	C-Chroman-2yl-methyl-amine	557	7.9	1E (Hydro)
159pb		25b	C-(1,2,3,4-Tetra-hydro-naphthalen-2-yl-)-methyl-amine	555	8.47	1E (Hydro)
159qb		25b	C-(2,3-Dihydro-benzo-furan-2yl)-methyl-amine	543	7.4	1E (Hydro)

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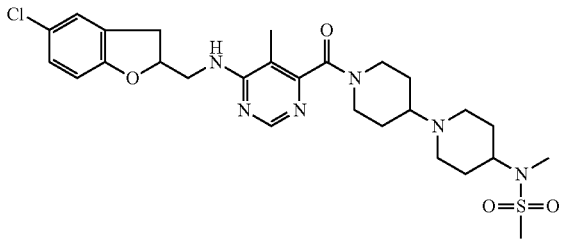
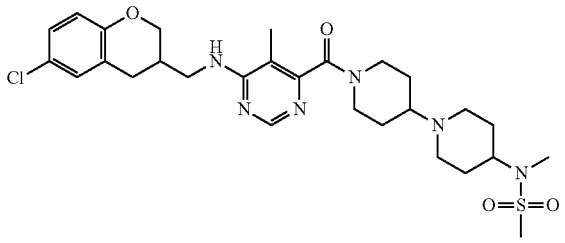
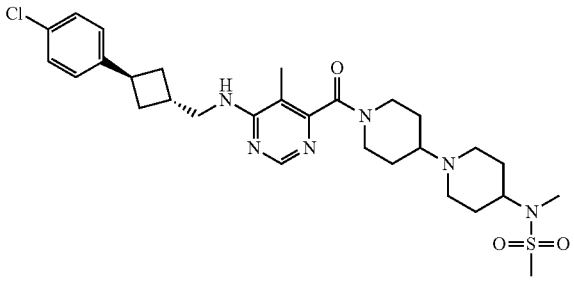
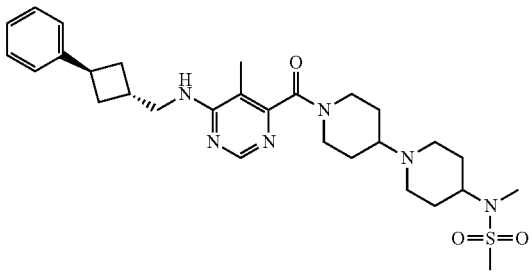
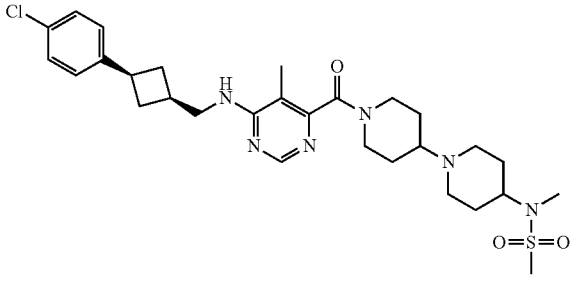
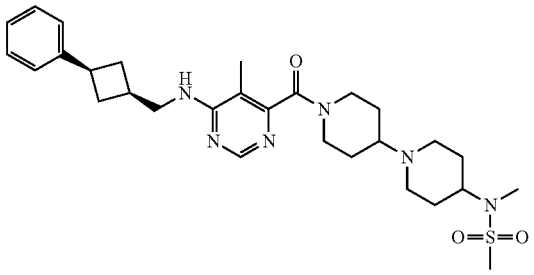
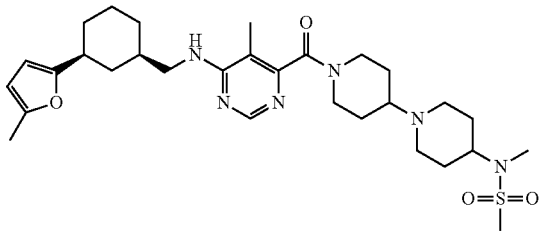
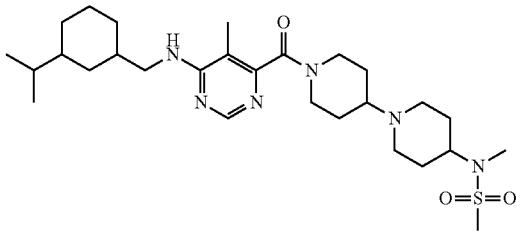
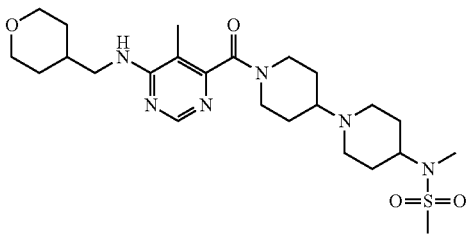
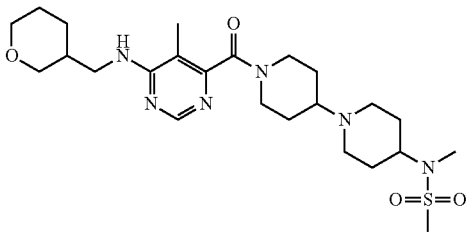
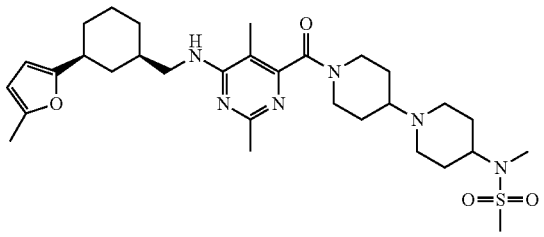
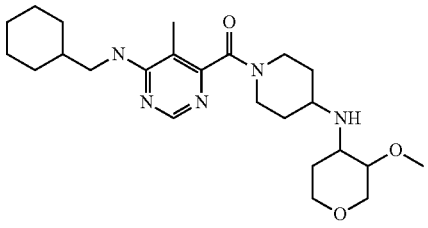
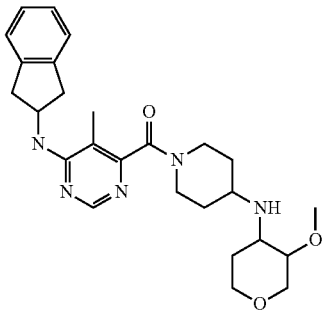
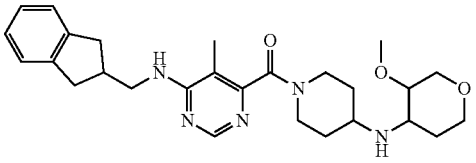
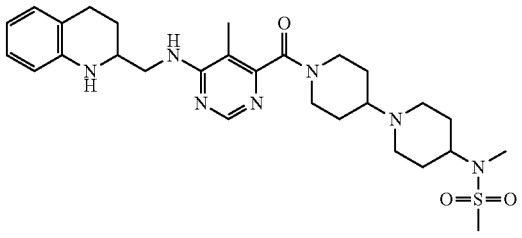
Ex #	STRUCTURE	Intermediate	Amine	[M + H]+	HPLC R_t (min)	Method
159rb		25b	C-(5-Chloro-2,3-Dihydro-benzo-furan-2yl)-methyl-amine	557	6.5	2F
159sb		25b	C-(6-Chloro-croman-3-yl)-methyl-amine	591	8.09	1E (Hydro)
159tb		25b	7s	589	9.8	1E (Hydro)
159ub		25b	7t	555	9.07	1E (Hydro)
159wb		25b	7u	589	9.7	1E (Hydro)

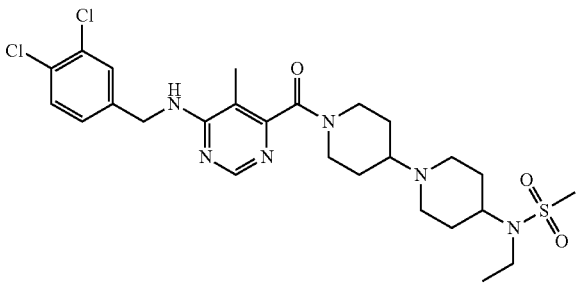
-continued

Ex #	STRUCTURE	Intermediate	Amine	$[M + H]^+$	HPLC R_t (min)	Method
159yb		25b	7v	555	9.02	1E (Hydro)
159xb		25b	7o	587	9.55	1E (Hydro)
159zb		25b	7k	549	10.37	1E (Hydro)
159ac		25b	C-(tetra-hydro-pyran-4-yl)-methyl-amine	509	5.92	1E (Hydro)
159bc		25b	C-(tetra-hydro-pyran-3-yl)-methyl-amine	509	6.15	1E (Hydro)
159cc		25l	7o	601	5.40	2M

-continued

Ex #	STRUCTURE	Intermediate	Amine	$[M + H]^+$	HPLC R_t (min)	Method
159dc		25o	C-cyclohexyl-methyl-amine	446	1.23	2Gb
159ec		25o	Indan-2-yl-amine	466	1.24	2Gb
159fc		25o	C-Indan-2-yl-methyl-amine	480	2.97	2Ga
159gc		25b	C-(1,2,3,4-Tetra-hydro-quinolin-2-yl)-methyl-amine	556	1.35	2Ca

Example 160

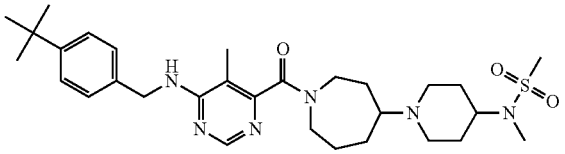
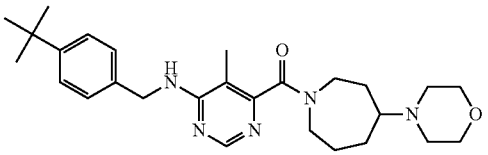
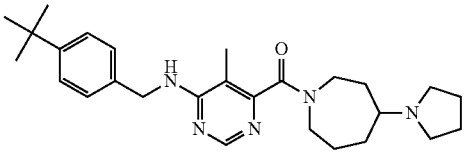
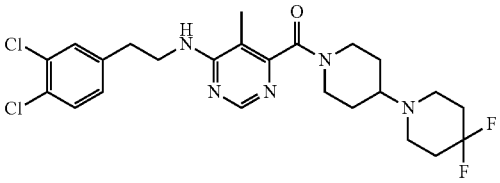
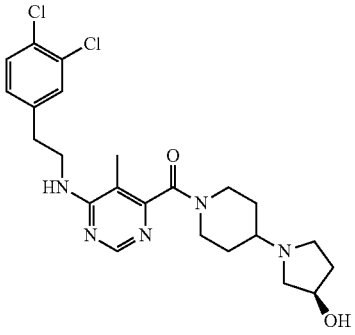
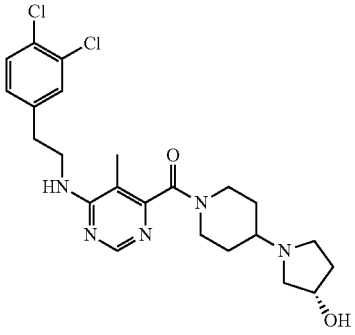


Intermediate 28b (80 mg, 0.20 mmol), Intermediate 13 (74 mg, 0.30 mmol) and N,N-diisopropyl-ethylamine (0.087 ml, 0.51 mmol) in 2 ml of dichloromethane were stirred at room temperature for 10 min Sodium triacetoxyborohydride (129 mg, 0.61 mmol) was added and the reaction mixture was stirred at room temperature overnight. The organic phase was washed with an aqueous saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by reverse phase preparative HPLC. 39 mg (0.06 mmol) of the desired product were obtained.

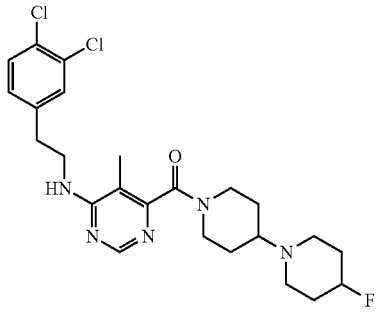
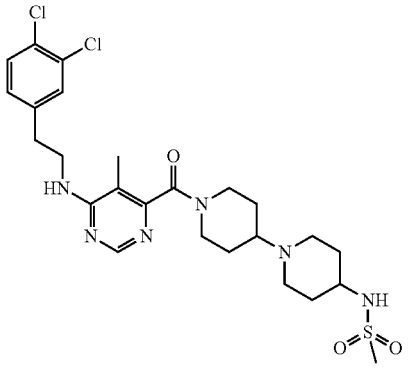
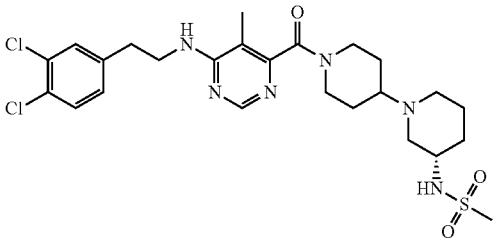
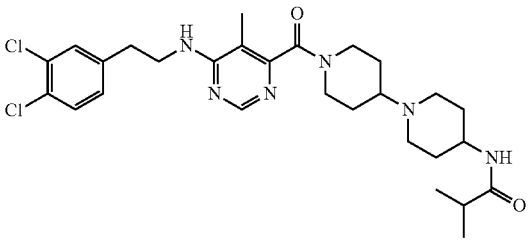
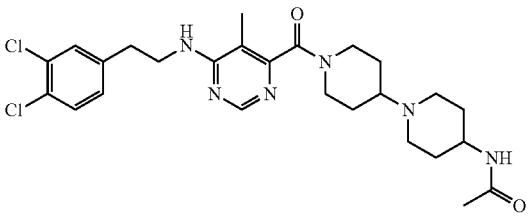
HPLC (Method 2F): R_t. (min)=7.25

$[M+H]^+$=583

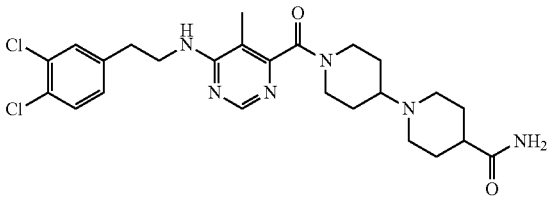
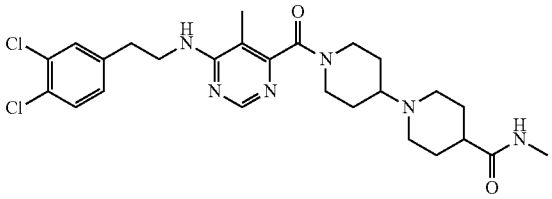
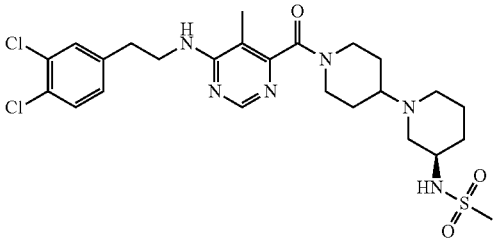
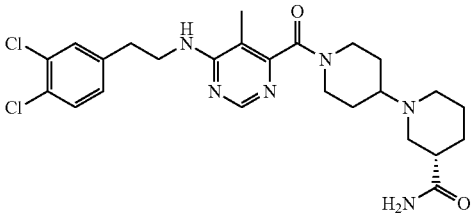
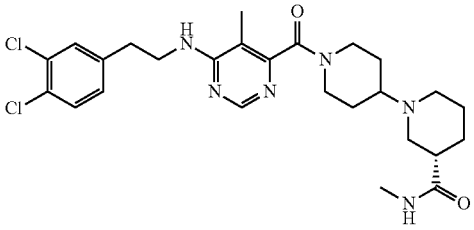
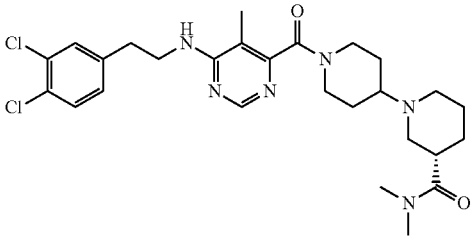
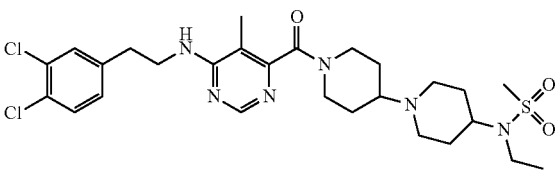
The following examples were synthesized in analogy to the preparation of Example 160.

Ex #	STRUCTURE	Inter-mediate	Amine or Ketone	$[M + H]^+$	HPLC R_t (min)	Method
161		28f	N-Methyl-N-piperidin-4-yl-methane-sulfon-amide	571	7.17	2F
162		28f	Morpho-line	466	9.97-10.27	1E
163		28f	Pyrroli-dine	450	7.06	2F
164		28a	4,4-difluoro-piperidine	512	8.17	1E
165		28a	(R)-pyrrolidin-3-ol	478	7.62	1E
166		28a	(S)-pyrrolidin-3-ol	478	7.57	1E

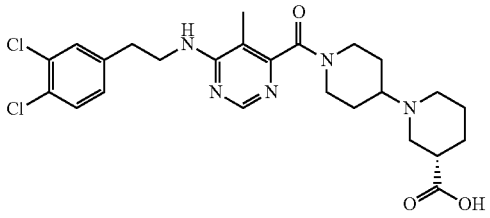
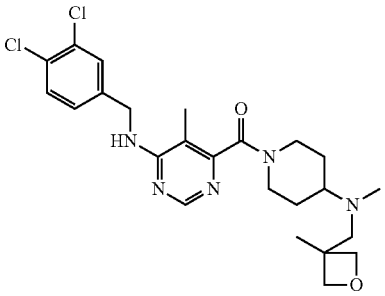
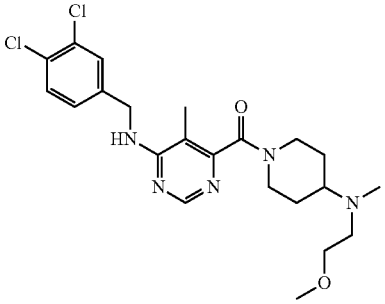
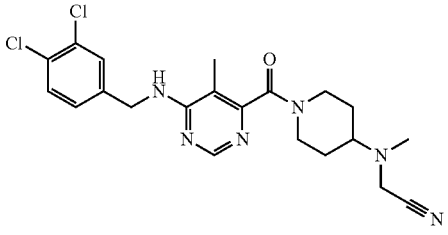
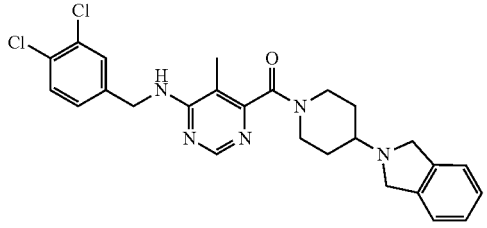
-continued

Ex #	STRUCTURE	Inter-mediate	Amine or Ketone	[M + H]+	HPLC R_t (min)	Method
167		28a	4-fluoro-piperidine	494	7.37	2F
168		28a	N-piperidin-4yl-methan-sulfon-amide	569	7.28	1E (Fusion)
169		28a	(S)-N-piperidin-3yl-methan-sulfon-amide	569	8.50	1E
170		28a	N-piperidin-4yl-isobutyr-amide	561	7.58	1E
171		28a	N-piperidin-4yl-acetamide	533	7.07	2F

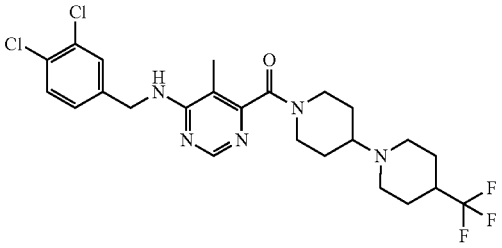
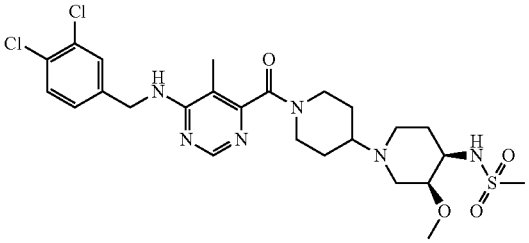
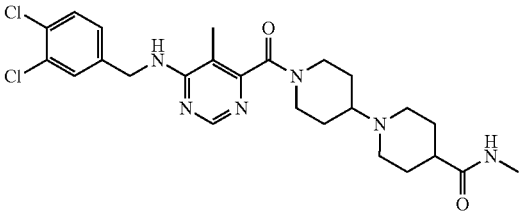
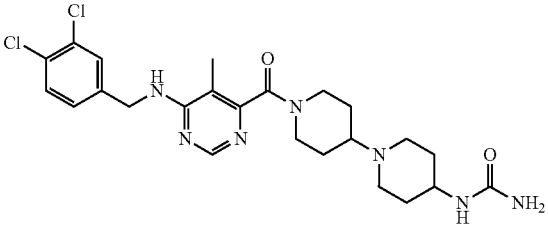
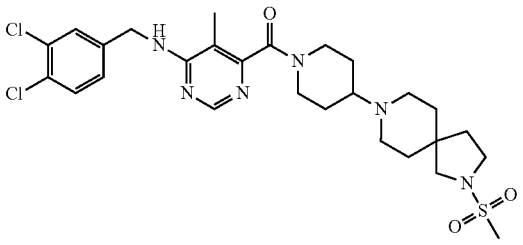
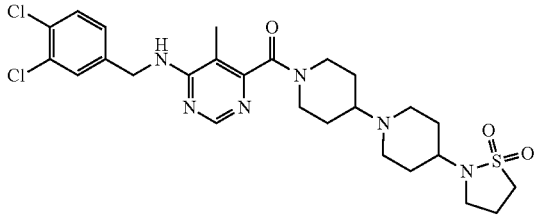
-continued

Ex #	STRUCTURE	Inter-mediate	Amine or Ketone	[M + H]+	HPLC R_t (min)	Method
172		28a	Piperidin-4-carboxylic acid amide	519	7.07	1E (Fusion)
173		28a	Piperidin-4-carboxylic acid methyl-amide	533	7.73	1E (Fusion)
174		28a	(R)-N-piperidin-3yl-methan-sulfon-amide	569	8.48	1E (Fusion)
175		28a	(S)-piperidine-3-carboxylic acid amide	519	8.70	1E (Fusion)
176		28a	(S)-piperidine-3-carboxylic acid methyl amide	533	7.03	2F
177		28a	(S)-piperidine-3-carboxylic acid dimethyl amide	547	7.15	2F
178		28a	N-Ethyl-N-piperidin-4-yl-methane-sulfon-amide	597	9.62	1E (Hydro)

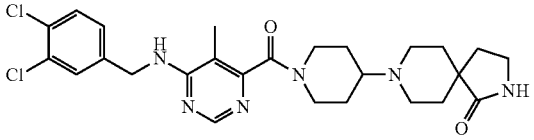
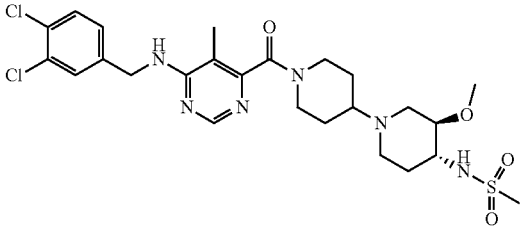
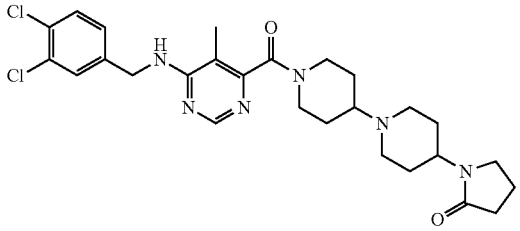
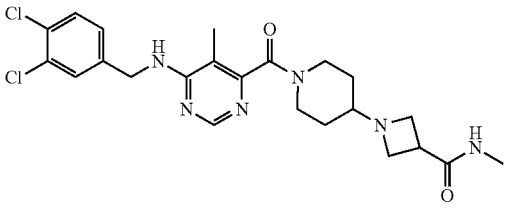
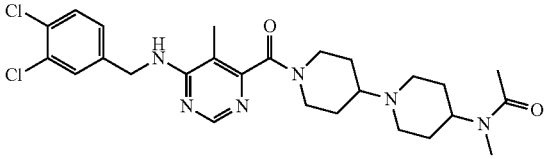
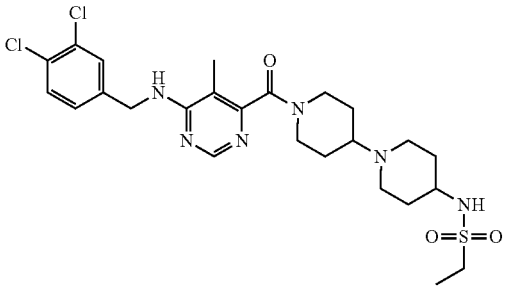
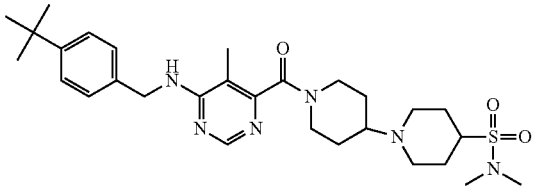
-continued

Ex #	STRUCTURE	Inter-mediate	Amine or Ketone	[M + H]+	HPLC R_t (min)	Method
179		28a	(S)-piperidine-3-carboxylic acid	520	6.60	1E (Fusion)
180		28b	Methyl-(3-methyl-oxetan-3yl-methyl)-amine	492	8.05	1E (Hydro)
181		28b	2-(methoxy-ethyl)-methyl-amine	466	7.72	1E (Hydro)
182		28b	Methyl-amino-aceto-nitrile	447	8.00	1E (Hydro)
183		28b	2,3-dihyro-1H-isoindole	496	9.52	1E (Hydro)

-continued

Ex #	STRUCTURE	Inter-mediate	Amine or Ketone	$[M + H]^+$	HPLC R_t (min)	Method
184		28b	4-trifluoro-methyl-piperidine	530	9.60	1E (Hydro)
185		28b	18	585	7.33	1E (Hydro)
186		28b	Piperidin-4-carboxylic acid methyl-amide	519	7.42	1E (Hydro)
187		28b	Piperidin-4yl-urea	520	7.05	2F
188		28b	2-methansul-fonyl-2,8-diaza-spiro[4.5]-decane	595	8.32	1E (Hydro)
189		28b	4-(1,1-dioxo-iso-thiazolidin-2-yl)-piperidine	581	8.23	1E (Hydro)

-continued

Ex #	STRUCTURE	Inter-mediate	Amine or Ketone	$[M + H]^+$	HPLC R_t (min)	Method
190		28b	2,8-diazaspiro [4.5]decan-1-one	531	7.58	1E (Hydro)
191		28b	16a	585	7.65	1E (Hydro)
192		28b	1-piperidin-4-yl-pyrrolidin-2-one	545	8.08	1E (Hydro)
193		28b	Azetidin-3-carboxylic acid methyl-amide	491	7.55	1E (Hydro)
194		28b	N-methyl-N-piperidin-4yl-acetamide	533	7.87	1E (Hydro)
195		28b	Ethan-sulfonic acid-piperidin-4-yl-amide	569	8.15	1E (Hydro)
196		28c	Piperidine-4-sulfonic acid dimethyl-amide	557	9.11	1E (Hydro)

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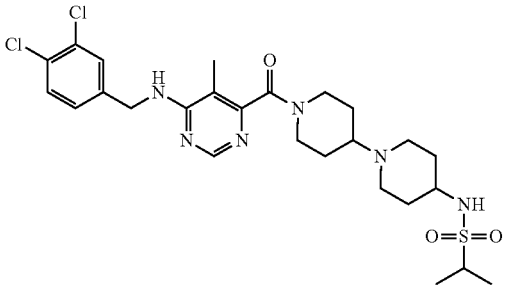
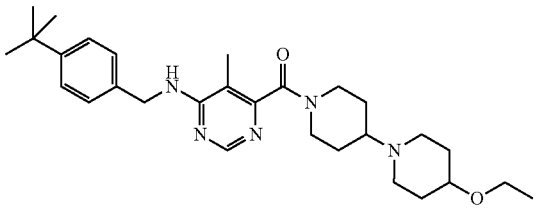
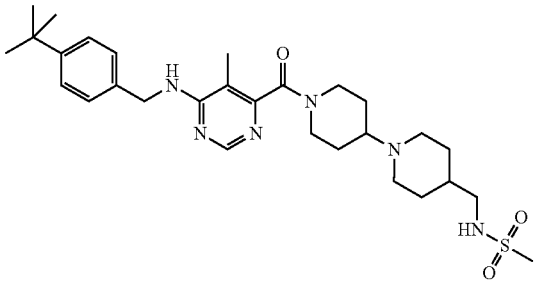
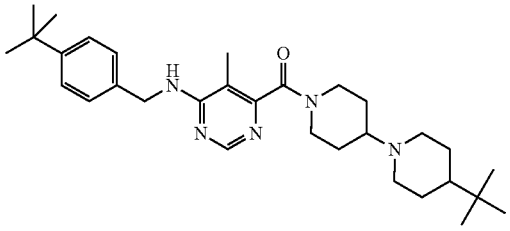
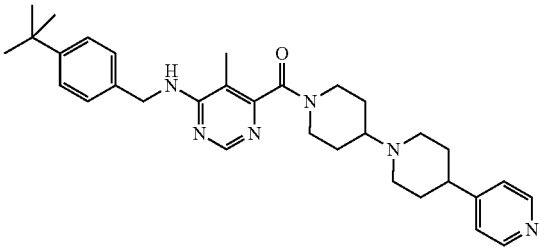
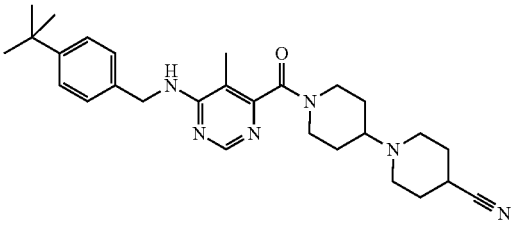
Ex #	STRUCTURE	Inter-mediate	Amine or Ketone	$[M + H]^+$	HPLC R_t (min)	Method
197		28b	Propan-2-sulfonic acid-piperidin-4-yl-amide	583	8.37	1E (Hydro)
198		28c	4-ethoxy-piperidine	494	10.75	1E (Hydro)
199		28c	N-piperidin-4-methyl-methan-sulfon-amide	557	9.45	1E (Hydro)
200		28c	4-tert-butyl-piperidine	506	7.86	2F
201		28c	4-(piperidin-4-yl)-pyridine	527	10.88	1E (Hydro)
202		28c	Piperidine-4-carbo-nitrile	475	9.77	1E (Hydro)

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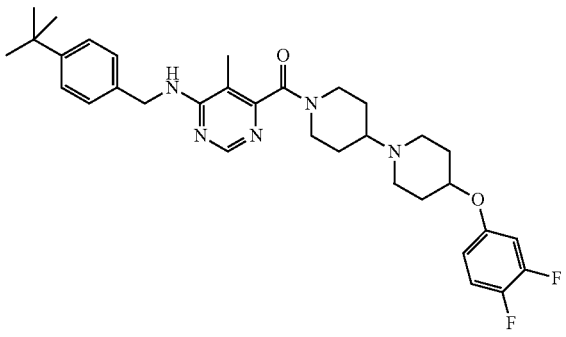
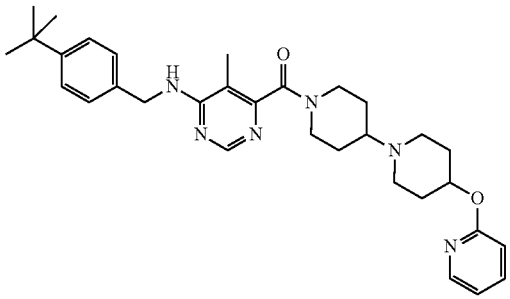
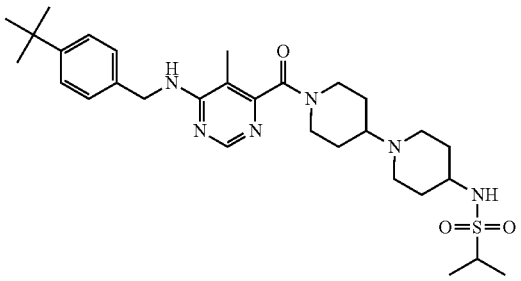
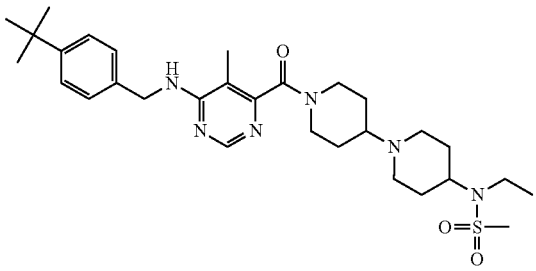
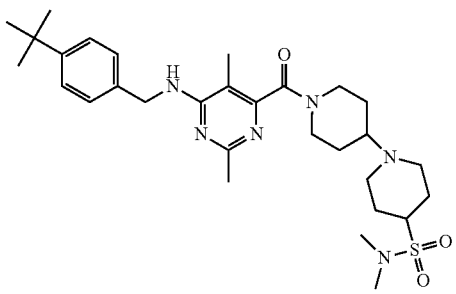
Ex #	STRUCTURE	Inter-mediate	Amine or Ketone	[M + H]+	HPLC R_t (min)	Method
203		28c	4-(3,4-difluoro-phenoxy)-piperidine	578	11.05	1E (Hydro)
204		28c	2-(piperidin-4-yloxy)-pyridine	543	10.38	1E (Hydro)
205		28c	Propan-2-sulfonic-acid-piperidin-4-yl-amide	571	9.12	1E (Hydro)
206		28	N-Ethyl-N-piperidin-4-yl-methane-sulfon-amide	571	10.18	1E (Hydro)
207		28g	Piperidine-4-sulfonic acid dimethyl-amide	571	9.67	1E (Hydro)

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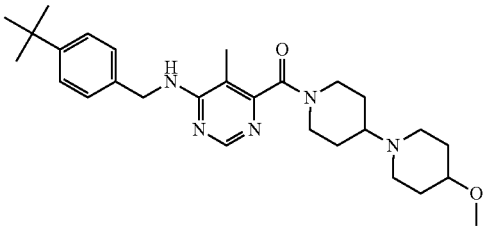
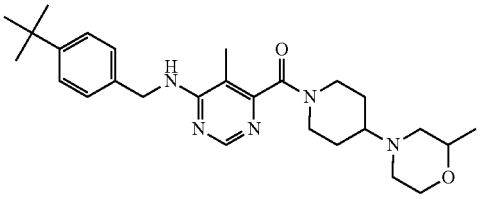
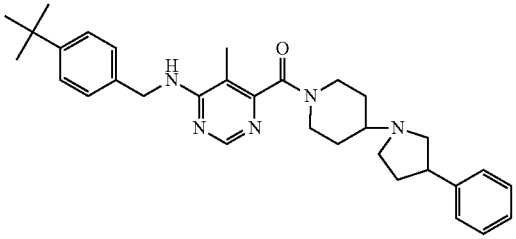
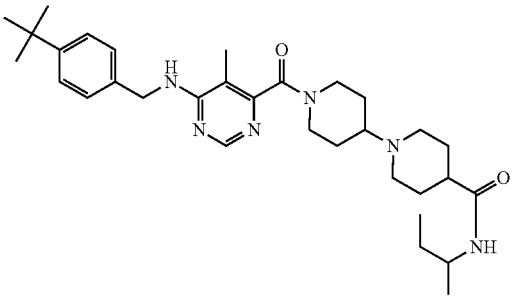
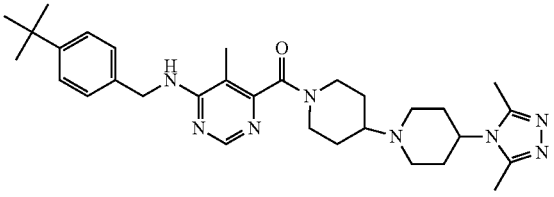
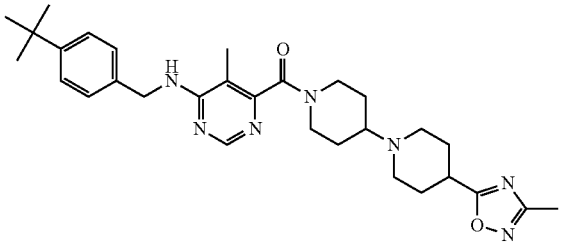
Ex #	STRUCTURE	Inter-mediate	Amine or Ketone	$[M + H]^+$	HPLC R_t (min)	Method
208		28c	4-methoxy-piperidine	480	2.21	2G
209		28c	2-methyl-morpho-line	466	3.46	2F
210		28c	3-Phenyl-pyrroli-dine	512	9.68	2F
211		28c	Piperidin-4-carboxylic acid sec-butyl amide	549	9.53	1E (Hydro)
212		28c	4-(3,5-dimethyl-[1,2,4]-triazol-4-yl)-piperidine	545	8.93	1E (Hydro)
213		28c	4-(3-methyl-[1,2,4]-oxadiazol-5-yl)-piperidine	532	8.21	2F

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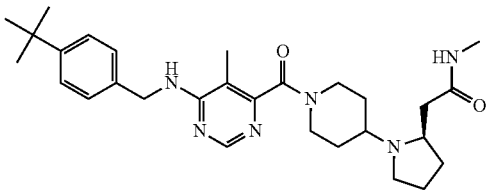
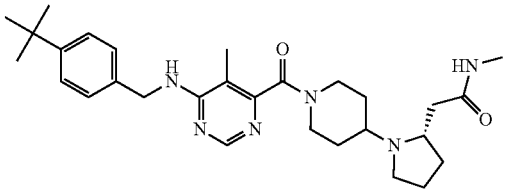
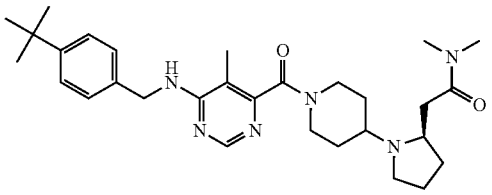
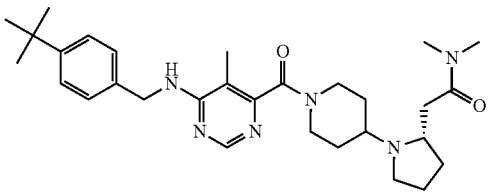
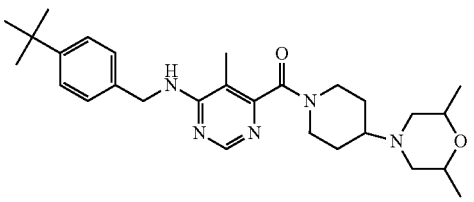
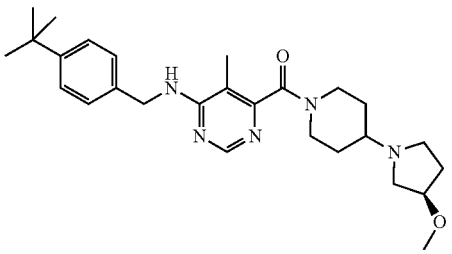
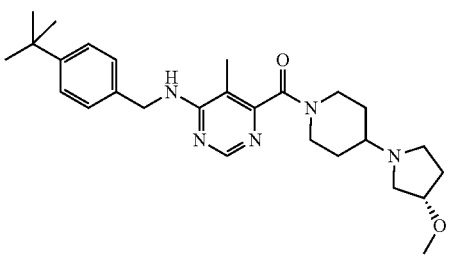
Ex #	STRUCTURE	Inter-mediate	Amine or Ketone	$[M + H]^+$	HPLC R_t (min)	Method
214		28c	N-methyl-2-(R)-(pyrrolidin-2-yl) acetamide	507	9.35	1E (Hydro)
215		28c	N-methyl-2-(S)-(pyrrolidin-2-yl) acetamide	507	9.24	1E (Hydro)
216		28c	N,N-dimethyl-2-(R)-(pyrrolidin-2-yl) acetamide	521	9.71	1E (Hydro)
217		28c	N,N-dimethyl-2-(S)-(pyrrolidin-2-yl) acetamide	521	9.72	1E (Hydro)
218		28c	2,6-dimethyl-morpho-line	480	8.92	2F
219		28c	(R)-3-methoxy-pyrroli-dine	466	7.23	2F
220		28c	(S)-3-methoxy-pyrroli-dine	466	7.23	2F

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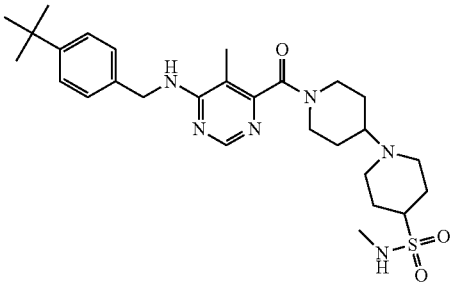
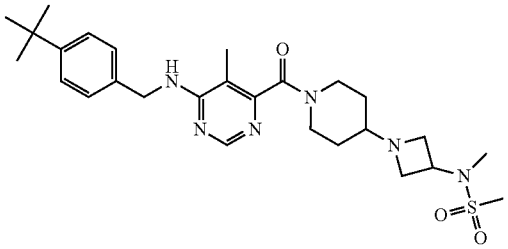
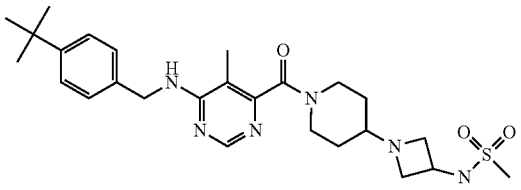
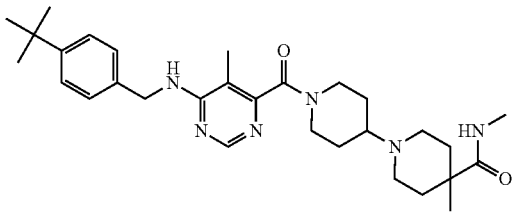
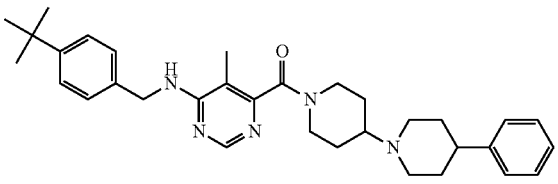
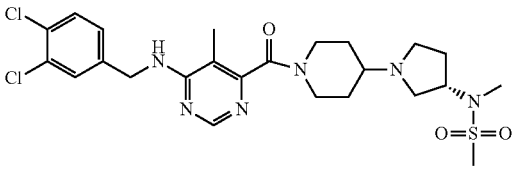
Ex #	STRUCTURE	Inter-mediate	Amine or Ketone	$[M + H]^+$	HPLC R_t (min)	Method
221		28c	Piperidine-4-sulfonic acid methyl-amide	543	8.50	1E (Hydro)
222		28c	N-azetidin-3-yl-N-methyl-methane-sulfon-amide	529	8.65	1E (Hydro)
223		28c	N-azetidin-3-yl-methane-sulfon-amide	515	8.02	1E (Hydro)
224		28c	4-methyl-piperidine-4-carboxylic acid methyl-amide	521	9.00	1E (Hydro)
225		28c	4-phenyl-piperidine	526	10.83	1E (Hydro)
226		28b	N-methyl-N-(S)-(pyrrolidin-3yl)-methane-sulfon-amide	555	8.04	1E (Hydro)

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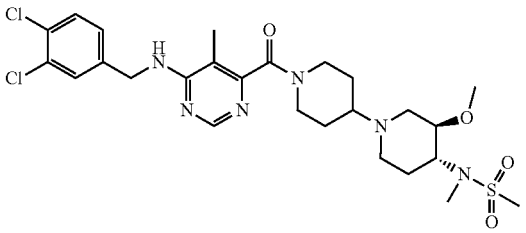
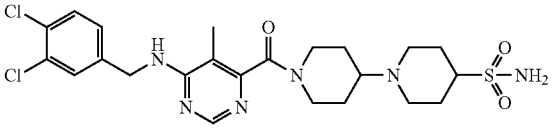
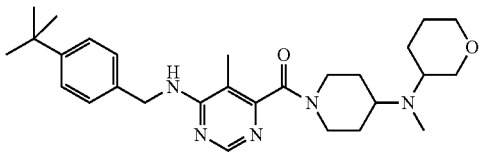
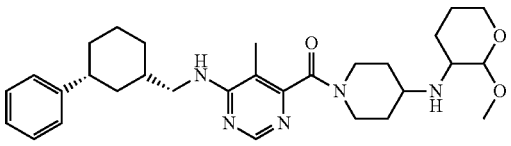
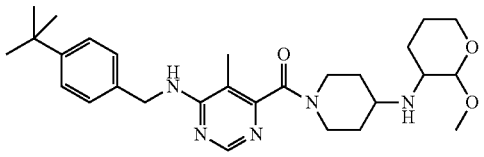
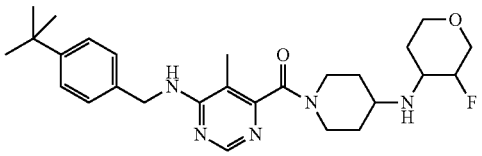
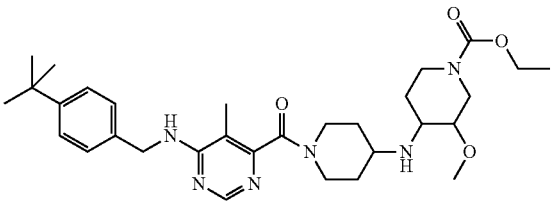
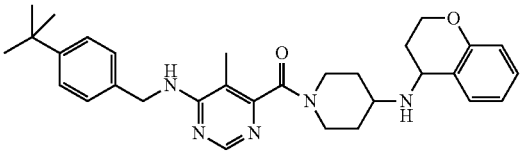
Ex #	STRUCTURE	Inter-mediate	Amine or Ketone	$[M + H]^+$	HPLC R_t (min)	Method
227		28b	16b	599	8.13	1E (Hydro)
228		28b	Piperidine-4-sulfonic acid amide	541	7.12	1E (Hydro)
228a		28c	Methyl-(tetra-hydro-pyran-3-yl)-amine	480	10.05	1E (Hydro)
228b		41b	3-methoxy-tetrahydro-pyran-4-one	522	9.25	1E (Hydro)
228c		41a	3-methoxy-tetrahydro-pyran-4-one	496	8.87	1E (Hydro)
228d		41a	3-fluoro-tetrahydro-pyran-4-one	484		1E (Hydro)
228e		41a	N-carb-ethoxy-3-methoxy-4-piperidone	567	7.42	2F
228f		41a	4-chromanone	514	10.31	1E (Hydro)

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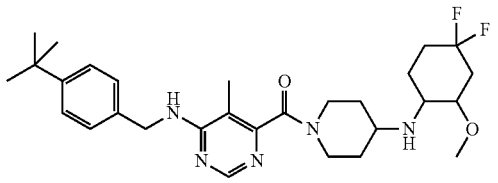
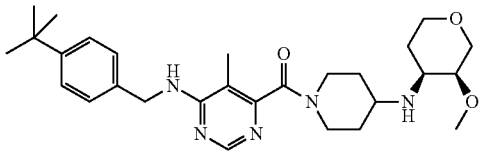
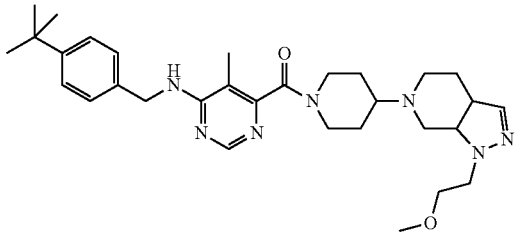
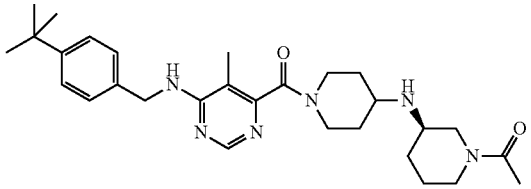
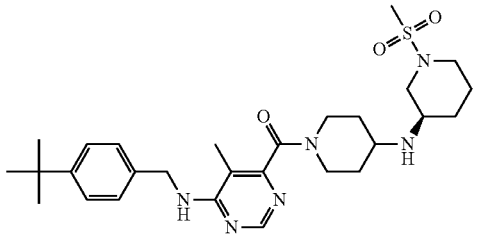
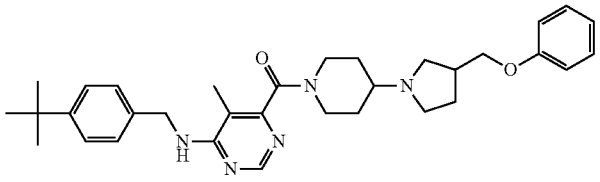
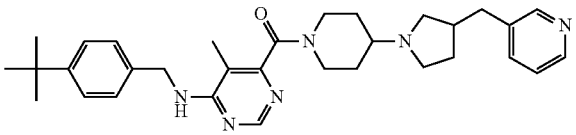
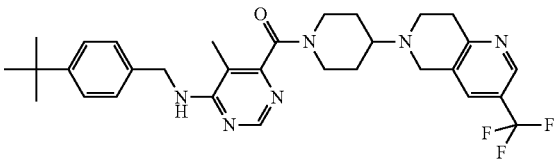
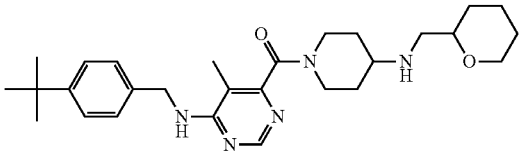
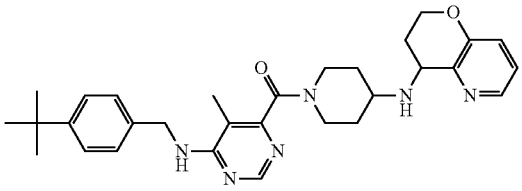
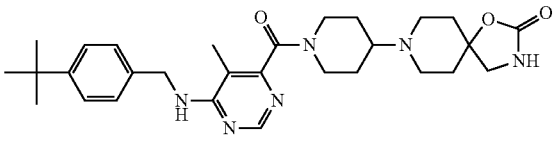
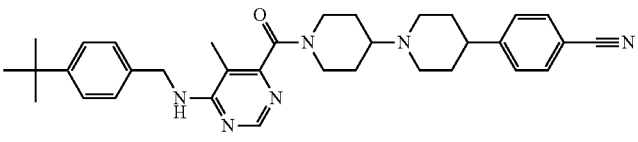
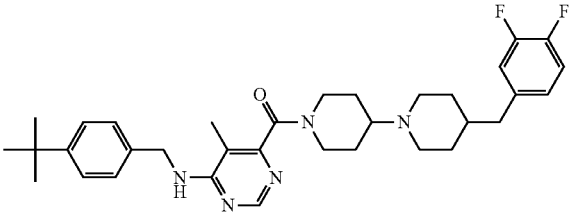
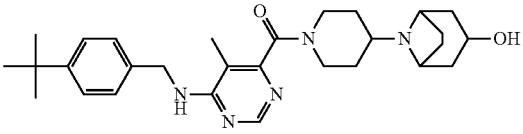
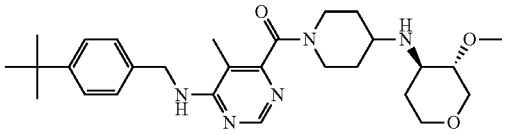
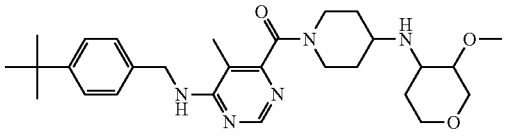
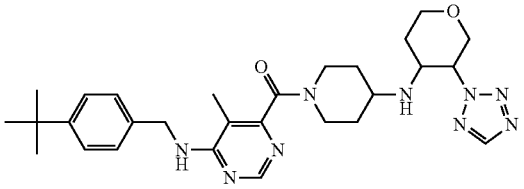
Ex #	STRUCTURE	Inter-mediate	Amine or Ketone	$[M + H]^+$	HPLC R_t (min)	Method
228g		41a	43	530	9.76	1E (Hydro)
228ga		28c	47a	496	5.77	2M
228gb		28c	1-(2-Methoxy-ethyl)-3a,4,5,6,7,7a-hexahydro-1H-pyrazolo-[3,4-c]pyridine	546	9.55	1E (Hydro)
228gc		28c	1-((R)-3-Amino-piperidin-1-yl)-ethanone	507	8.85	1E (Hydro)
228gd		28c	(R)-1-Methane-sulfonyl-piperidin-3-yllamine	543	9.11	1E (Hydro)
228ge		28c	3-Phenoxy-methyl-pyrrolidine	542	10.92	1E (Hydro)
228gf		28c	3-Pyrrolidin-3-yl-pyridine	527	10.00	1E (Hydro)
228gg		28c	3-Trifluoro-methyl-5,6,7,8-tetrahydro-[1,6]naph-thyridine	567	7.69	2F

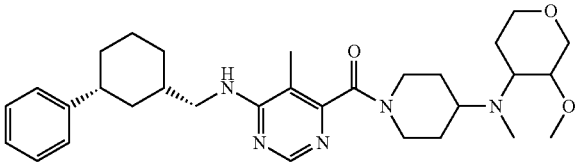
-continued

Ex #	STRUCTURE	Inter-mediate	Amine or Ketone	$[M + H]^+$	HPLC R_t (min)	Method
228gh		28	C-(Tetrahydro-pyran-2-yl)methyl-amine	480	2.09	2Cb
228gi		28c	56	515	2.18	2Cb
228gj		28c	1-Oxa-3,8-diaza-spiro[4,5] decan-2-one	521	8.30	1E (Hydro)
228gk		28c	4-Piperidin-4-yl-benzonitrile	551	10.35	1E (Hydro)
228gl		28c	4-(3,4-Difluoro-benzyl)-piperidine	576	11.42	1E (Hydro)
228gm		28c	8-Aza-bicyclo[3.2.1]octan-3-ol	492	9.30	1E (Hydro)

-continued

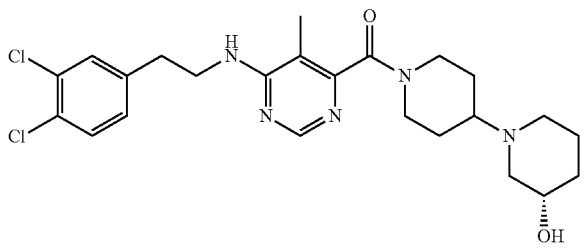
Ex #	STRUCTURE	Inter-mediate	Amine or Ketone	[M + H]+	HPLC R_t (min)	Method
228gn		28c	45	496	5.96	2M
228go		41a	3-Methoxy-tetrahydro-pyran-4-one	508	5.77	2M
228gp		41a	3-Tetrazol-2-yl-tetrahydro-pyran-4-one	534	7.09	2F

Example 228h



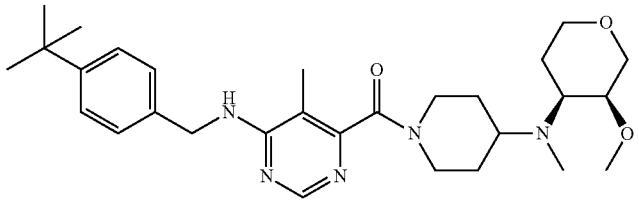
Example 228b (22 mg, 0.032 mmol), formaldehyde (0.003 ml, 0.096 mmol), N,N-diisopropyl-ethylamine (0.008 ml, 0.048 mmol) and trifluoroacetic acid (0.005 ml) in 1.5 ml of methanol were stirred at room temperature for 5 min. Sodium cyanoborohydride (10 mg, 0.160 mmol) was added and the reaction mixture was stirred at room temperature overnight. The organic phase was concentrated under vacuum. The crude product was purified by flash chromatography (Isolute silica gel cartridge 5 g, eluent: ethyl acetate/methanol=7:3%). 8.4 mg (0.016 mmol) of the desired product were obtained.

The following examples were synthesized in analogy to the preparation of Example 228h.



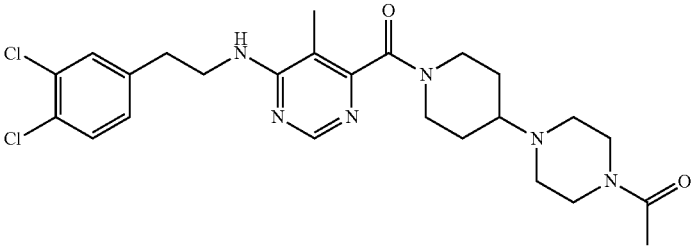
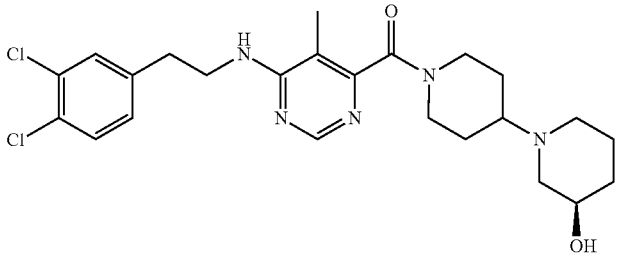
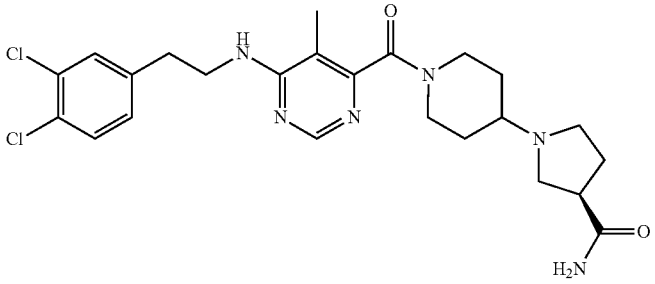
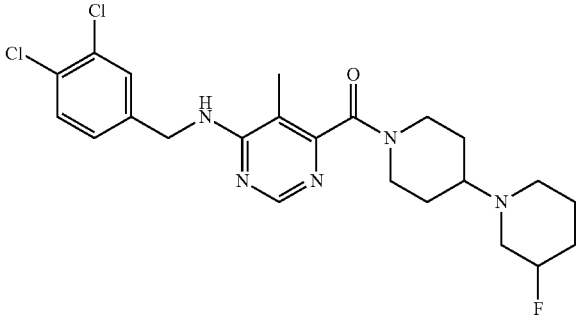
Example 229

Intermediate 28a (100 mg, 0.25 mmol), (S)-3-hydroxypiperidine (67 mg, 0.49 mmol) and trimethylorthoformate (1.07 ml, 9.82 mmol) in 5 ml of methanol were stirred at 60° C. for 1 h. 2-picoline borane complex (26 mg, 0.25 mmol) was added and the reaction mixture was stirred at 60° C. overnight. The reaction mixture was concentrated under vacuum. The crude product was purified by reverse phase preparative HPLC. 64 mg (0.13 mmol) of the desired product were obtained.

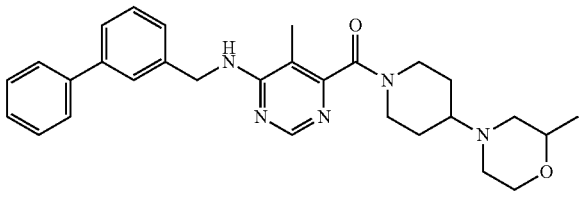
Ex #	STRUCTURE	Starting example	[M + H]+	HPLC R_t (min)	Method
228 ha		228ga	510	5.72	2M

HPLC (Method 1E): R_t. (min)=7.18
$[M+H]^+$=492

The following examples were synthesized in analogy to the preparation of Example 229.

Ex #	STRUCTURE	Inter-mediate	Amine	$[M + H]^+$	HPLC R_t. (min)	Method
230		28a	1-piperazin-1-yl-ethanone	519	7.13	2F
231		28a	(R)-piperidin-3-ol	492	7.35	1E (Fusion)
232		28a	(R)-pyrrolidin-3-carboxylic acid amide	505	7.83	1E (Fusion)
233		28b	3-fluoro-piperidine	480	8.32	1E (Hydro)

Example 234

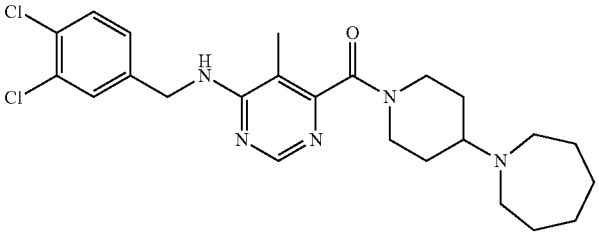
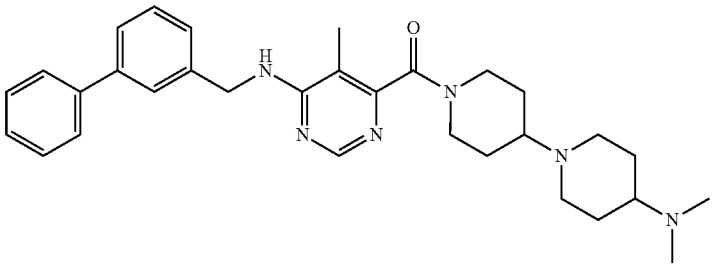
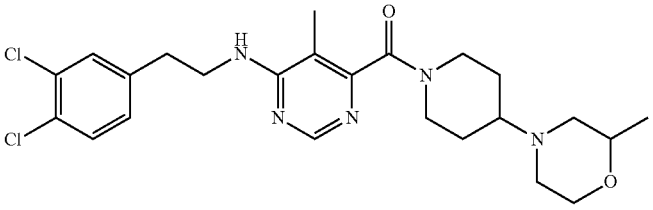
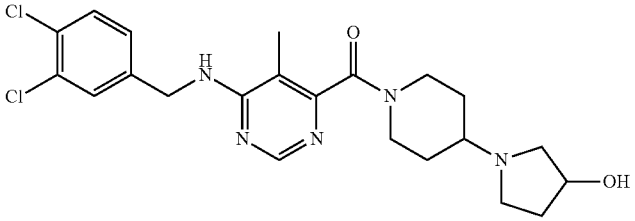
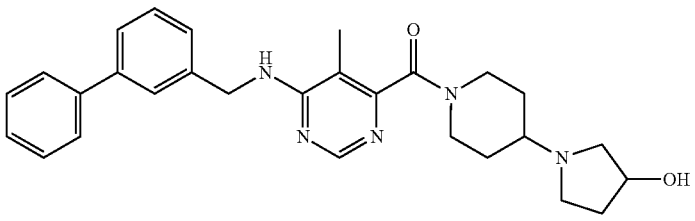


Intermediate 28d (20 mg, 0.05 mmol), 2-methyl-morpholine (0.012 ml, 0.10 mmol), sodium triacetoxyborohydride (43 mg, 0.20 mmol), acetic acid (0.05 ml) and trimethylorthoformate (0.05 ml) in 0.9 ml of DMA were stirred at room temperature for 3 h. The reaction mixture was concentrated under vacuum. The crude product was purified by reverse phase preparative HPLC. 3 mg (0.006 mmol) of the desired product were obtained.

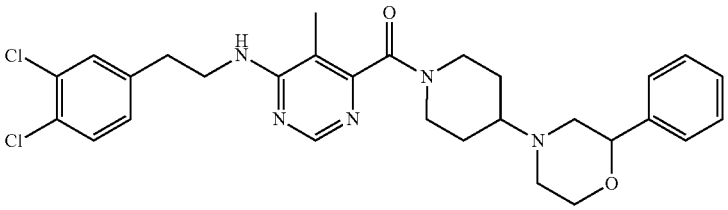
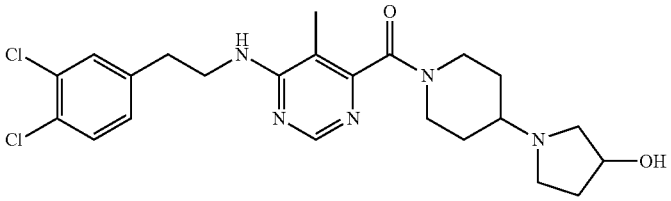
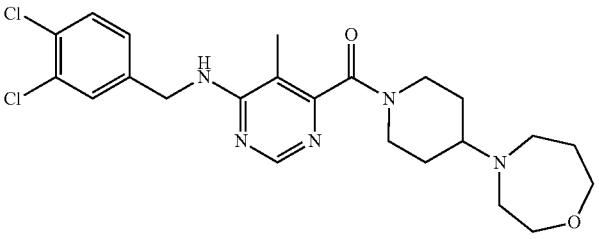
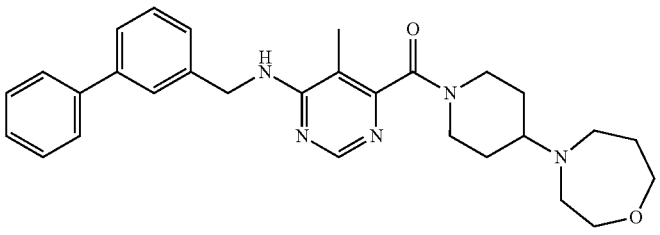
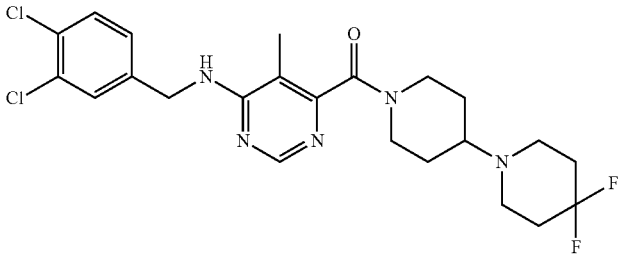
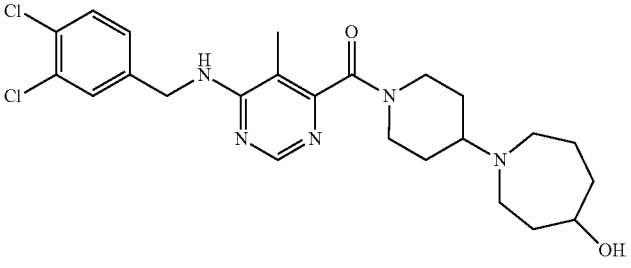
HPLC (Method A): R_t. (min)=1.74

$[M+H]^+$=486

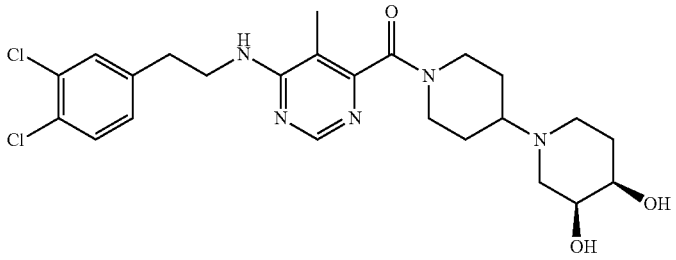
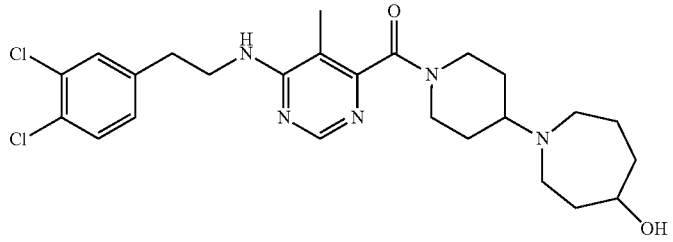
The following examples were synthesized in analogy to the preparation of Example 234.

Ex #	STRUCTURE	Intermediate	Amine	$[M+H]^+$	HPLC R_t. (min)	Method
235		28b	Azepane	476	1.72	2A
236		28d	Dimethyl-piperidin-4yl-amine	513	1.64	2A
237		28a	2-methyl-morpholine	492	1.72	2A
238		28b	Pyrrolidin-3-ol	464	1.65	2A
239		28d	Pyrrolidin-3-ol	472	1.71	2A

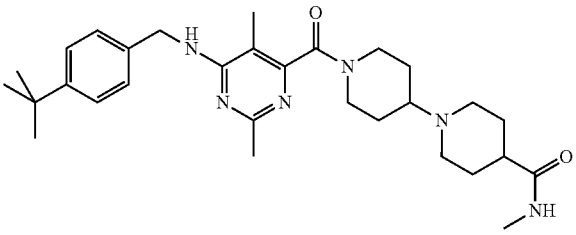
-continued

Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R_t (min)	Meth-od
240		28a	2-phenyl-morpho-line	554	1.84	2A
241		28a	Pyrrolidin-3-ol	478	1.68	2A
242		28b	[1,4]-oxazepane	478	1.66	2A
243		28d	[1,4]-oxazepane	486	1.72	2A
244		28b	4,4-difluoro-piperidine	498	1.72	2A
245		28b	Azepan-4-ol	492	1.65	2A

-continued

Ex #	STRUCTURE	Intermediate	Amine	[M + H]+	HPLC R_t (min)	Method
246		28a	(3S,4R)-piperidine-3,4-diol	508	1.66	2A
247		28a	Azepan-4-ol	506	1.68	2A

Example 248

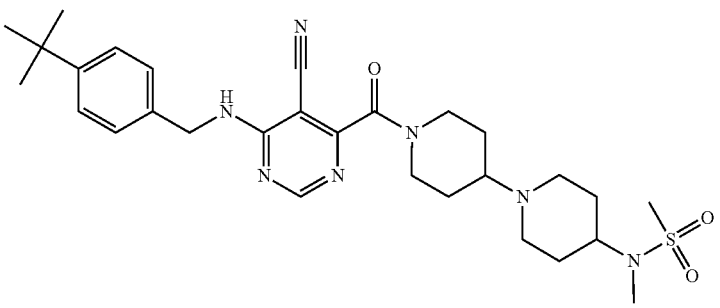


Intermediate 27e (105 mg, 0.33 mmol), TBTU (215 mg, 0.67 mmol) and N,N-diisopropyl-ethylamine (0.12 ml, 0.67 mmol) in 2 ml DMF were stirred at room temperature for 5 min Intermediate 20f (100 mg, 0.33 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum and the crude product was dissolved in dichloromethane. The organic phase was washed with an aqueous saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Si Isolute cartridge (5 g); eluent: ethyl acetate/methanol=90/10%). 30 mg (0.057 mmol) of the desired product were obtained.

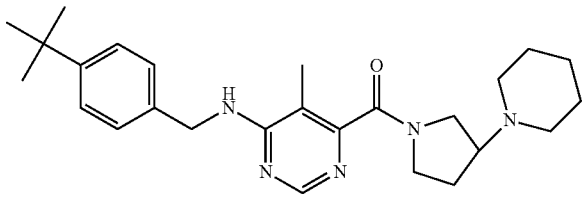
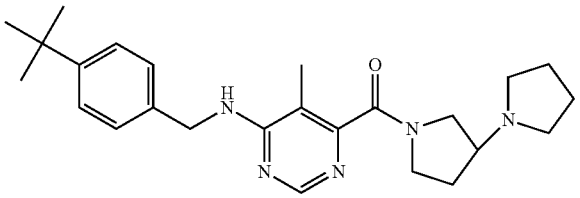
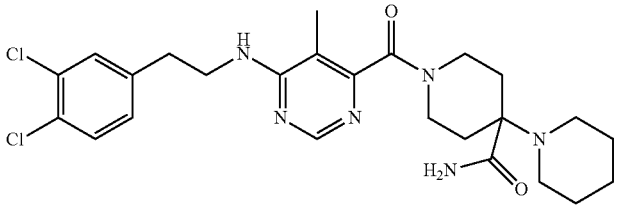
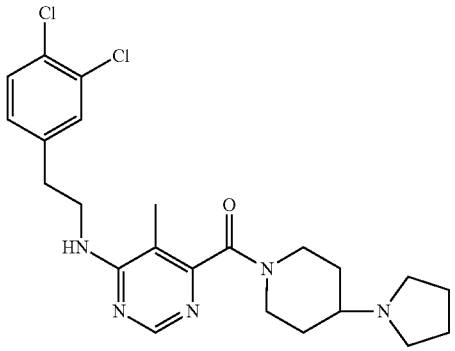
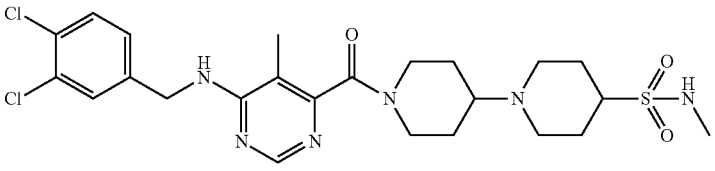
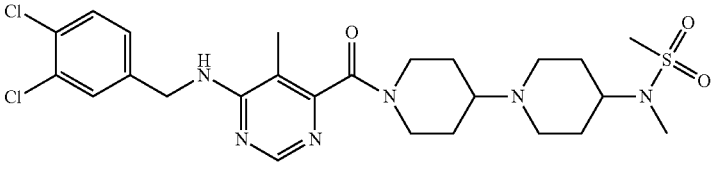
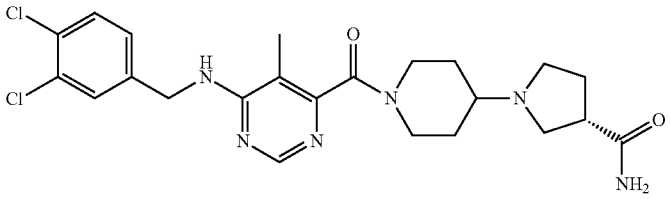
HPLC (Method 1E Hydro): R_t (min)=9.2

$[M+H]^+$=521

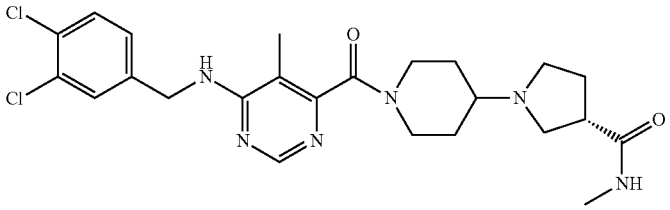
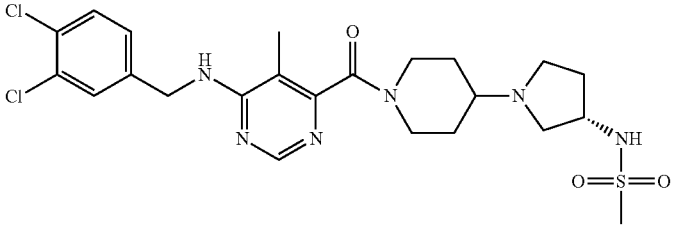
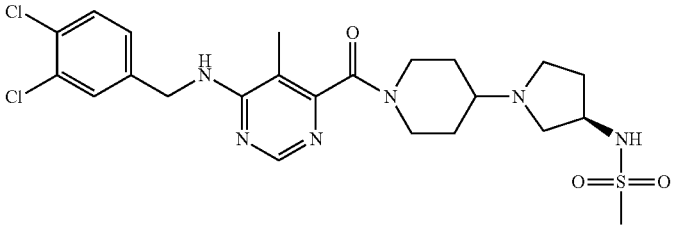
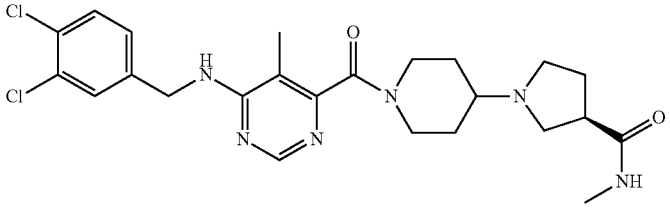
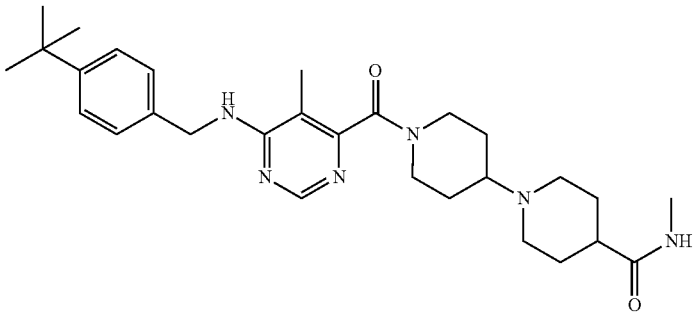
The following examples were synthesized in analogy to the preparation of Example 248.

Ex #	STRUCTURE	Intermediate	Amine	[M + H]+	HPLC R_t (min)	Method
249		27i	20a	568	10.07	1E (Hydro)

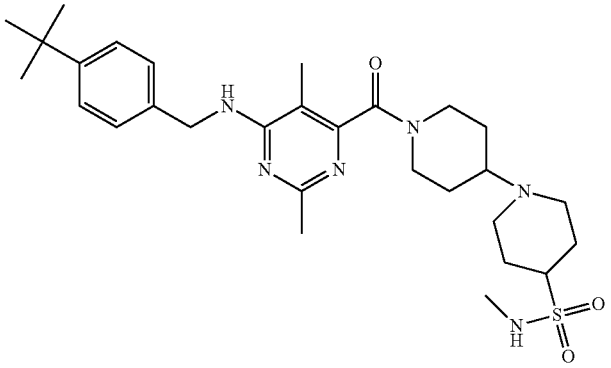
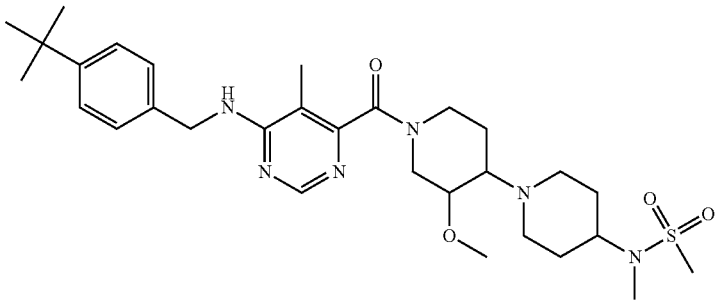
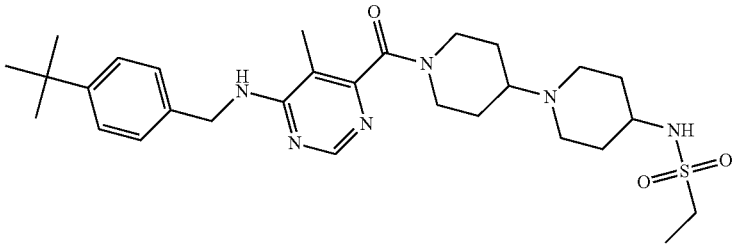
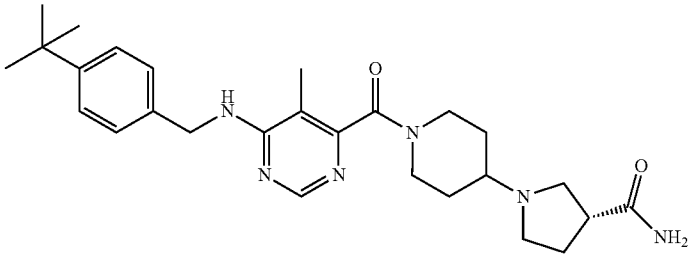
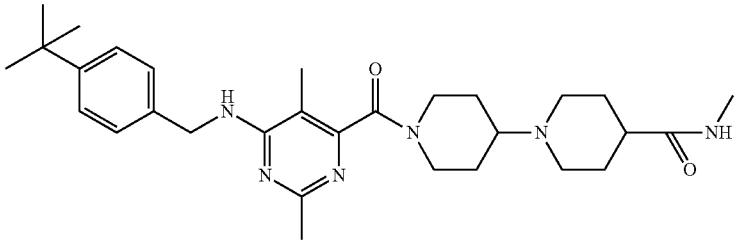
-continued

Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R_t (min)	Meth-od
250		27c	1-pyrrolidin-3-yl-piper-idine	436	1.5	1E (Hy-dro)
251		27c	[1,3']-Bipyrro-lidinyl	422	10.35	1E (Hy-dro)
252		27a	[1,4']-Bipiper-idinyl-4' car-boxylic-acid amide	519	8.60	1E (Fu-sion)
253		27a	4-pyrroli-din-1yl-piper-idine	462	7.07	2F
254		27b	20g	555	7.50	1E (Hy-dro)
255		27b	20a	569	8.15	1E (Hy-dro)
256		27b	20j	491	7.03	1E (Hy-dro)

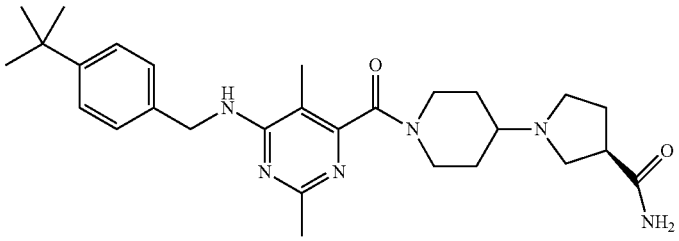
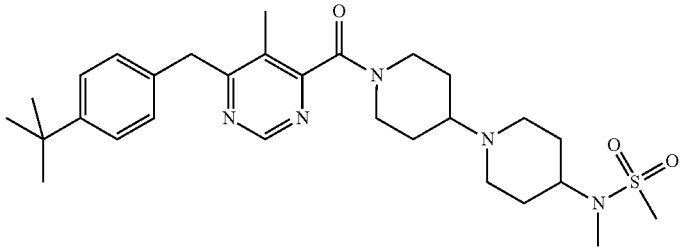
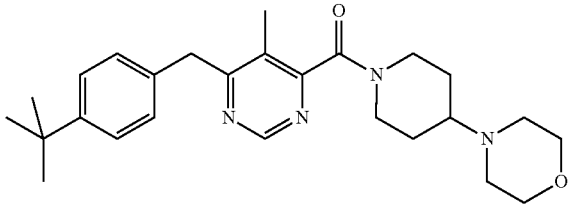
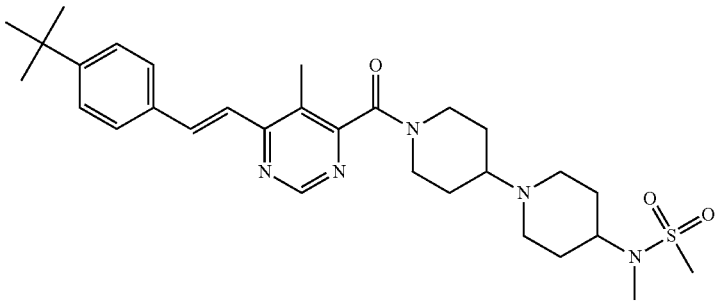
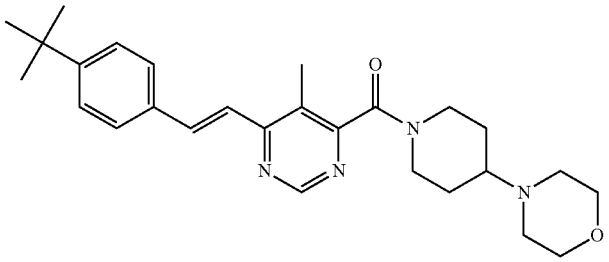
-continued

Ex #	STRUCTURE	Inter-me-diate	Amine	[M + H]+	HPLC R_t (min)	Meth-od
257		27b	20i	505	7.43	1E (Hy-dro)
258		27b	20d	541	7.50	1E (Hy-dro)
259		27b	20c	541	7.48	1E (Hy-dro)
260		27b	20h	505	7.85	1E (Hy-dro)
261		27c	20f	507	8.70	1E (Hy-dro)

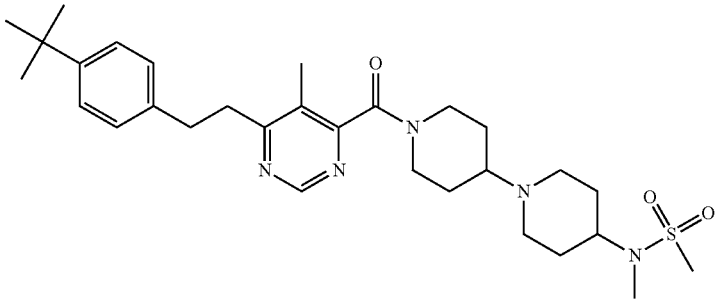
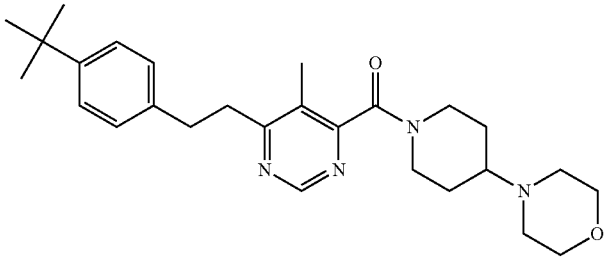
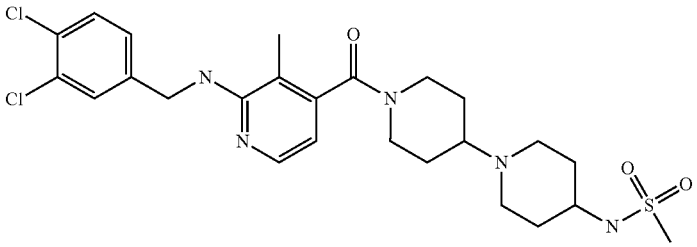
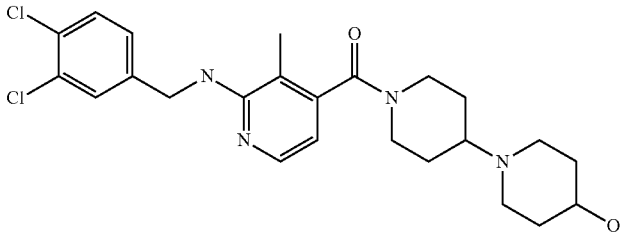
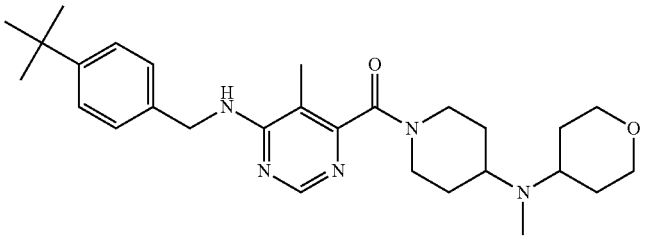
-continued

Ex #	STRUCTURE	Inter-me-diate	Amine	[M + H]+	HPLC R_t (min)	Meth-od
262		27e	20g	557	9.11	1E (Hy-dro)
263		27c	20m	587	8.79	2F
264		27c	20e	557	8.85	1E (Hy-dro)
265		27c	20l	479	8.37	1E (Hy-dro)
266		27e	20f	521	9.2	1E (Hy-dro)

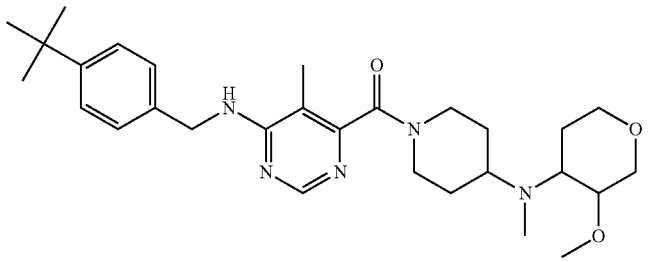
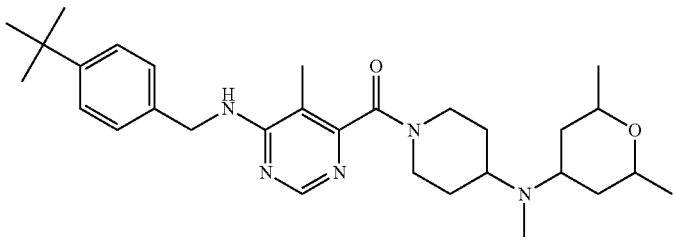
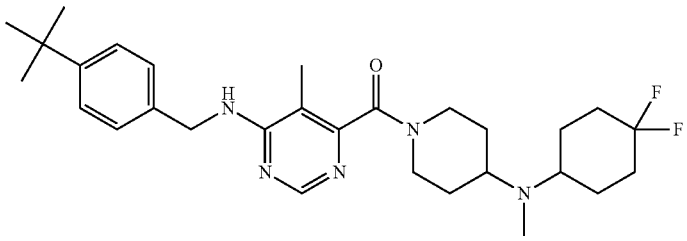
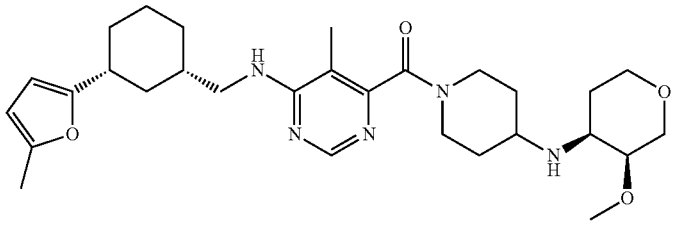
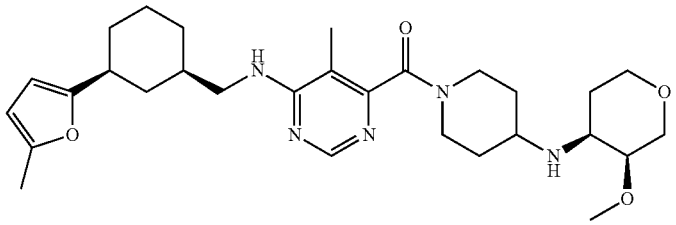
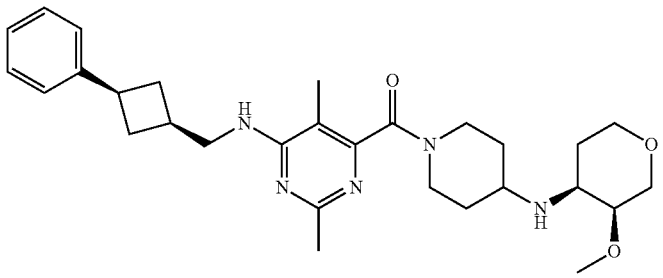
-continued

Ex #	STRUCTURE	Inter-me-diate	Amine	[M + H]$^+$	HPLC R_t (min)	Meth-od
267		27e	20l	493	8.93	1E (Hy-dro)
268		39b	20a	542	3.54	2F
269		39b	4-piper-idin-4-yl-morpho-line	436	7.43	2F
270		39a	20a	553	8.28	2F
271		39a	4-piper-idin-4-yl-morpho-line	449	7.60	2F

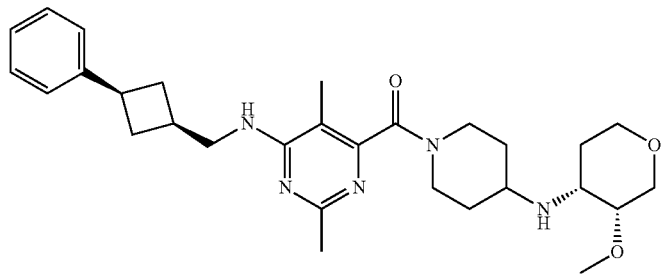
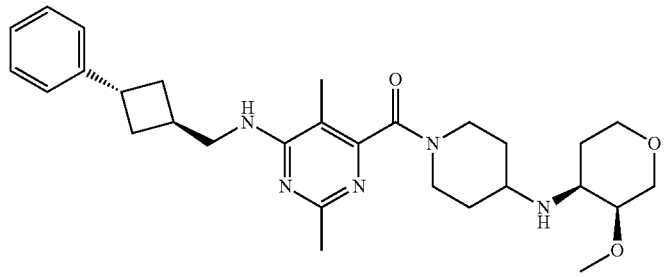
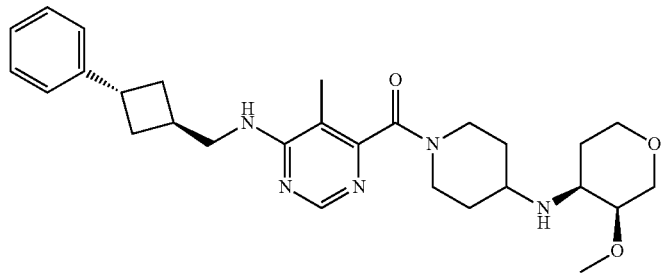
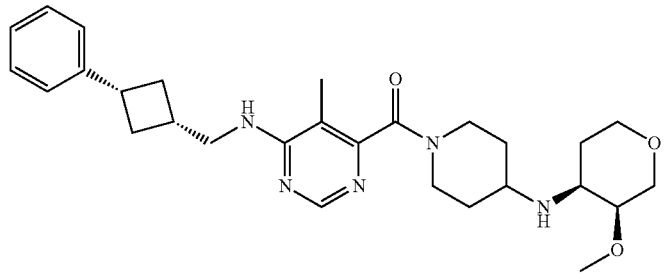
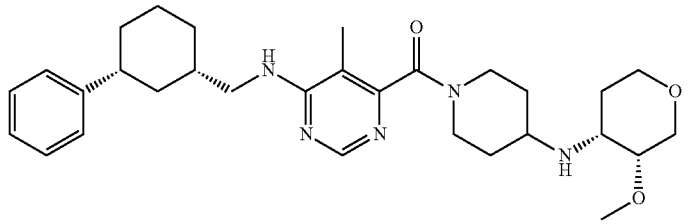
-continued

Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R_t (min)	Method
272		39c	20a	556	7.98	2F
273		39c	4-piperidin-4-yl-morpholine	450	7.29	2F
274		39d	24	554	8.28	1E (Hydro)
275		39d	[1,4']-bipiperidinyl-4-ol	477	7.77	1E (Hydro)
275a		27c	20la	480	10.03	1E (Hydro)

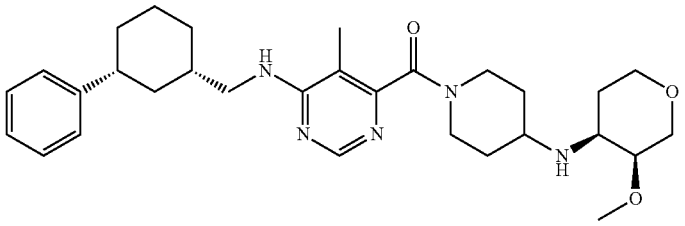
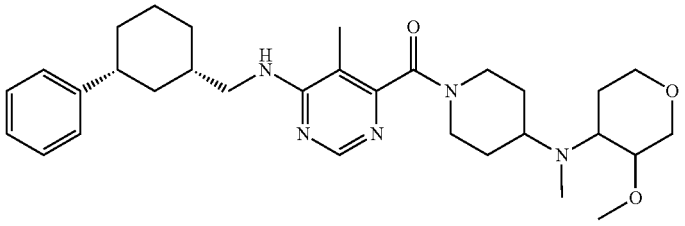
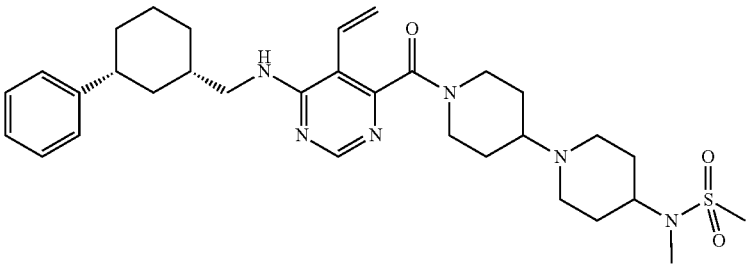
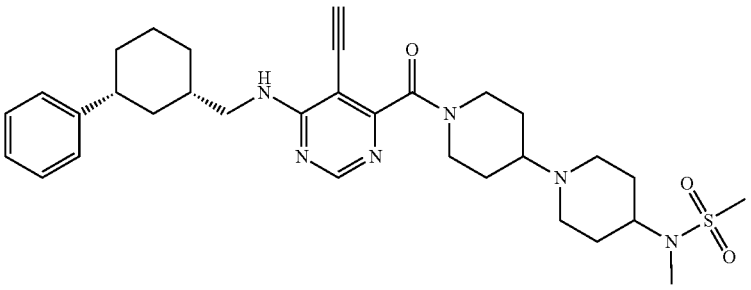
-continued

Ex #	STRUCTURE	Inter-me-diate	Amine	[M + H]$^+$	HPLC R_t (min)	Meth-od
275b		27c	20lb	510	9.48	1E (Hy-dro)
275c		27c	20lc	508	10.27	1E (Hy-dro)
275d		27c	20ld	514	10.13	1E (Hy-dro)
275da		27hc	20lg	526	9.16	1E (Hy-dro)
275db		27hd	20lg	526	9.18	1E (Hy-dro)
275dc		27hs	20lg	508	7.25	1F

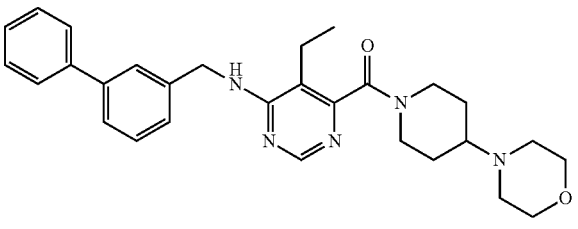
-continued

Ex #	STRUCTURE	Inter-me-diate	Amine	[M + H]+	HPLC R_t (min)	Meth-od
275dd		27hf	20lf	494	6.53	2F
275de		27hr	20lg	508	8.55	1E (Hy-dro)
275df		27he	20lg	494	8.07	1E (Hy-dro)
275dg		27hf	20lg	494	8.10	1E (Hy-dro)
275dh		27ha	20lf	522	9.03	1E (Hy-dro)

-continued

Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R_t (min)	Meth-od
275di		27ha	20lg	522	9.00	1E (Hydro)
275dj		27ha	20la	536	9.76	1E (Hydro)
275dk		27ib	20a	595	2.16	2Cb
275dl		27ic	20a	593	2.20	2Cb

Example 276

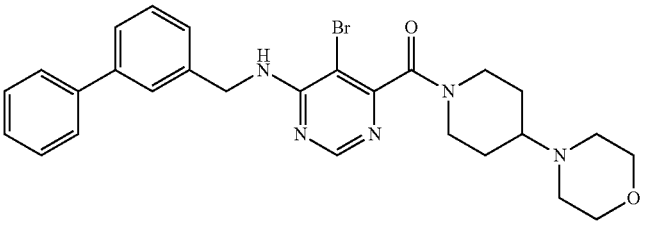
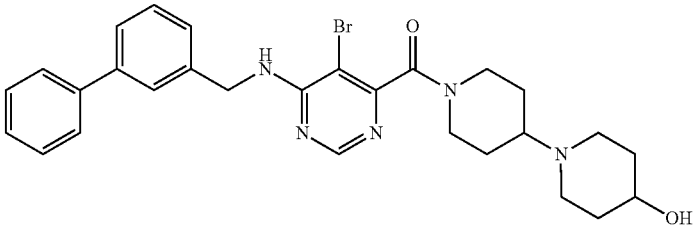
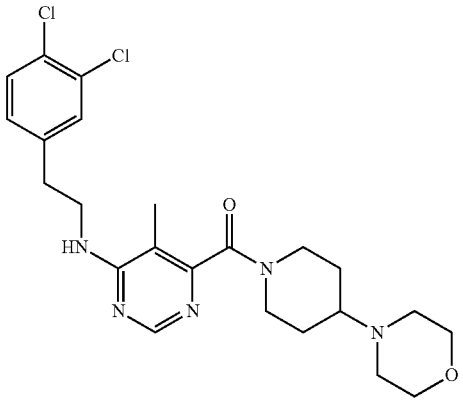
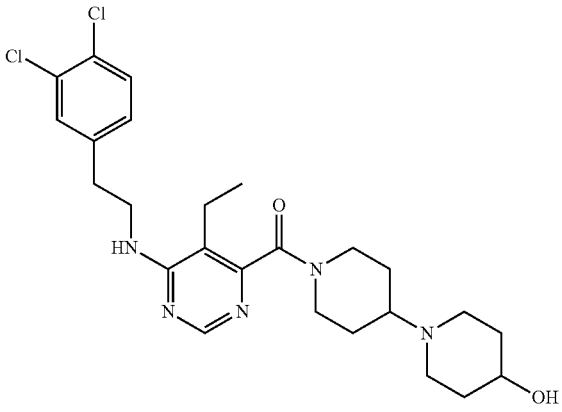


Intermediate 27g (50 mg, 0.14 mmol), HATU (55 mg, 0.14 mmol) and N,N-diisopropyl-ethylamine (0.05 ml, 0.28 mmol) in 2 ml DMF were stirred at room temperature for 5 min 4-piperidin-4-yl-morpholine (24 mg, 0.14 mmol) was added and the reaction mixture was stirred at room temperature 3 h. The reaction mixture was concentrated under vacuum and the crude product was dissolved in dichloromethane. The organic phase was washed with an aqueous saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by reverse phase preparative HPLC. 80 mg (0.13 mmol) of the desired product were obtained.

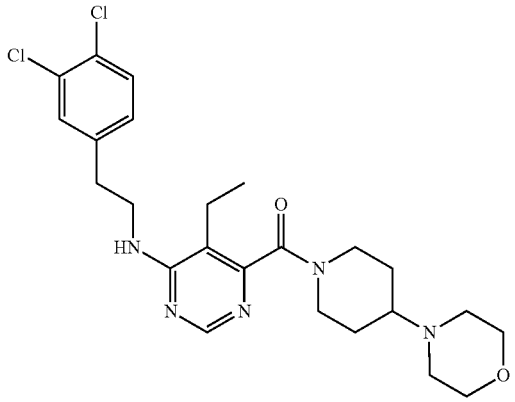
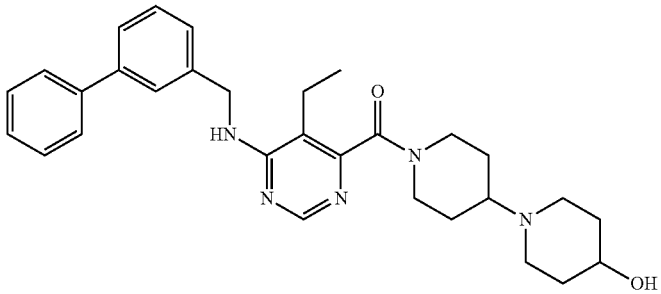
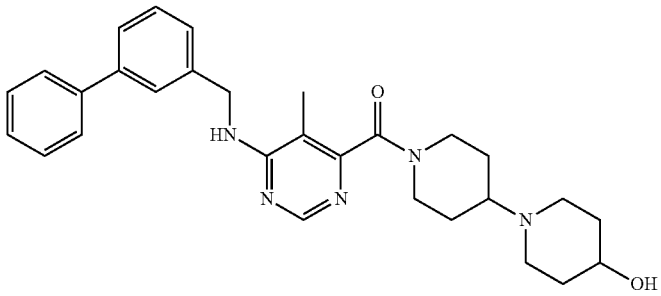
HPLC (Method C): R_t (min)=1.57

$[M+H]^+$=486

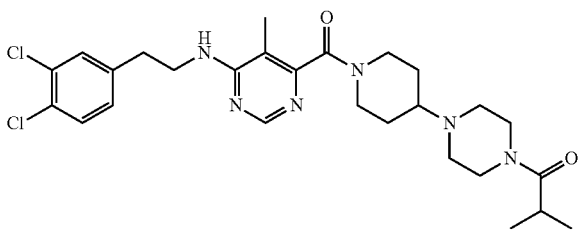
The following examples were synthesized in analogy to the preparation of Example 276.

Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R_t- (min)	Method
277		27h	4-piperidin-4-yl-morpholine	536	1.69	2C
278		27h	[1,4']-Bipiperidinyl-4-ol	550	1.65	2C
279		27a	4-piperidin-4-yl-morpholine	478	1.52	2C
280		27f	[1,4']-Bipiperidinyl-4-ol	506	1.52	2C

-continued

Ex #	STRUCTURE	Inter-mediate	Amine	[M + H]+	HPLC R_t (min)	Method
281		27f	4-piperidin-4-yl-morpholine	492	1.53	2C
282		27g	[1,4']-Bipiperidinyl-4-ol	500	1.55	2C
283		39e	[1,4']-Bipiperidinyl-4-ol	484	1.66	2C

Example 284

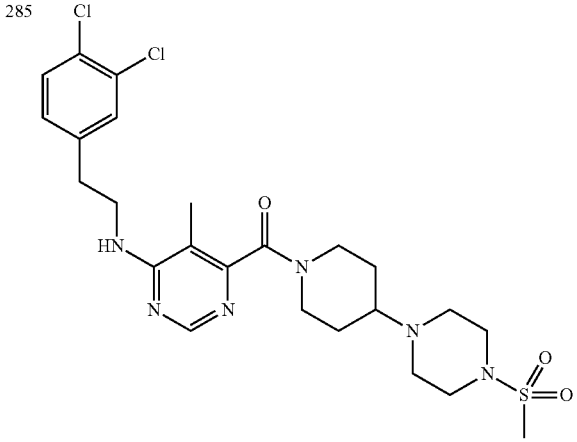


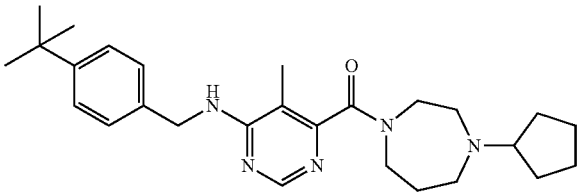
Intermediate 30 (45 mg, 0.088 mmol) and N,N-diisopropylethylamine (0.05 ml, 0.27 mmol were dissolved in 5 ml of dichloromethane. The reaction mixture was stirred at 0° C. and isobutyrylchloride (0.01 ml, 0.09 mmol) was added. The reaction mixture was stirred at 0° C. for 20 min, then it was washed with an aqueous saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was suspended and stirred in diisopropyl ether, the solid filtered off to obtain 30 mg (0.05 mmol) of the desired compound.

HPLC (Method 1E): R_t. (min)=7.02

$[M+H]^+$=547

The following examples were synthesized in analogy to the preparation of Example 284.

Ex #	STRUCTURE	Inter-mediate	Chloride	[M + H]+	HPLC Rt. (min)	Method
285		30	Methane-sulfonyl chloride	555	6.91	2F



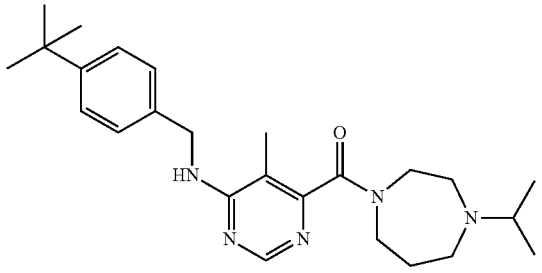
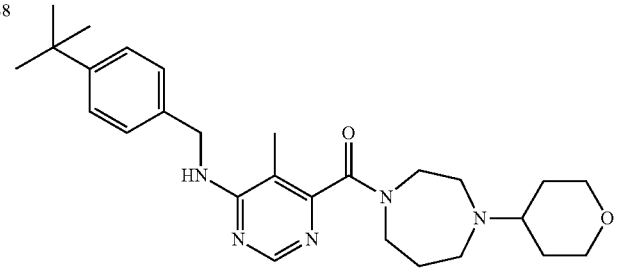
Example 286

Intermediate 32 (100 mg, 0.26 mmol) and cyclopentanone (0.02 ml, 0.26 mmol) in 2 ml of dichloromethane were stirred at room temperature for 10 min Sodium triacetoxyborohydride (132 mg, 0.62 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by reverse phase preparative HPLC. 31 mg (0.07 mmol) of the desired product were obtained.

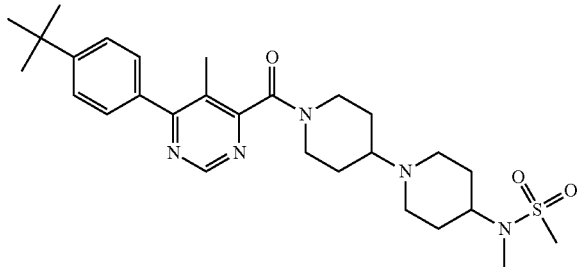
HPLC (Method 2F): R_t. (min)=7.52

$[M+H]^+$=450

The following examples were synthesized in analogy to the preparation of Example 286.

Ex #	STRUCTURE	Inter-mediate	Ketone	[M + H]+	HPLC Rt. (min)	Method
287		32	Acetone	424	7.24	2F
288		33	Tetrahydro-pyran-4-one	466	7.18	2F

Example 289

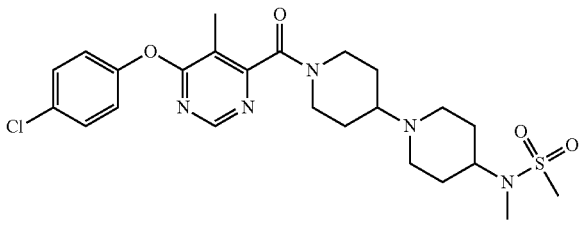


Intermediate 25b (200 mg, 0.46 mmol) 4-tert-butylphenylboronic acid (99 mg, 0.56 mmol), tetrakis(triphenylphosphine)palladium (53 mg, 0.05 mmol) and 0.56 ml of a 2M aqueous solution of sodium carbonate in 2 ml of 1,2-dimethoxyethane were stirred at 80° C. overnight. After cooling to room temperature, water was added and the reaction mixture was extracted with dichloromethane. The organic phase was washed with an aqueous saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Si Isolute cartridge (5 g); eluent: ethyl acetate/methanol=95/5%). 41 mg (0.08 mmol) of the desired product were obtained.

HPLC (Method 1E Hydro): R_t. (min)=9.93

$[M+H]^+$=528

Example 290

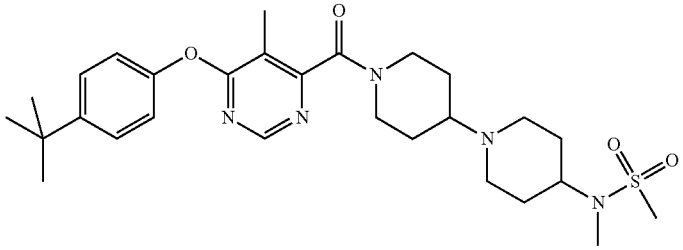


Intermediate 25b (60 mg, 0.14 mmol) and 4-chlorophenol (0.014 ml, 0.14 mmol) were dissolved in 2 ml of DMF. Cesium carbonate (45 mg, 0.14 mmol) was added and the reaction mixture was stirred at room temperature overnight. The solvent was concentrated under vacuum, the crude product was dissolved in dichloromethane and the organic phase was washed with water, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Si Isolute cartridge (5 g); eluent: dichloromethane/ethyl acetate=90/1%). 50 mg (0.09 mmol) of the desired product were obtained.

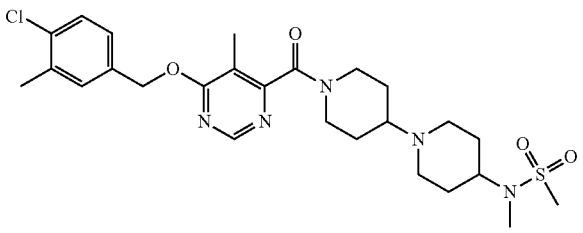
HPLC (Method 1E Hydro): R_t. (min)=8.9

$[M+H]^+$=522

The following example was synthesized in analogy to the preparation of Example 290.

Ex #	STRUCTURE	Inter-mediate	Phenol	[M + H]$^+$	HPLC R_t (min)	Method
291		25b	4-tertbutyl-phenol	544	7.64	2F

Example 292

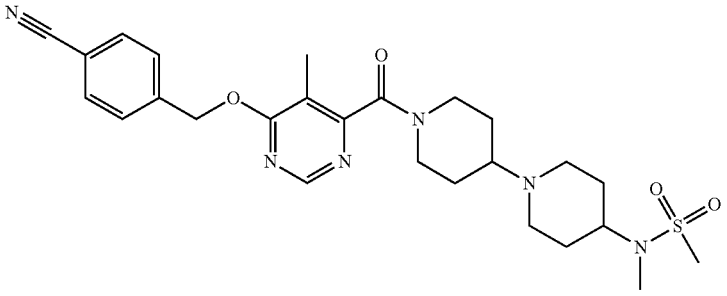
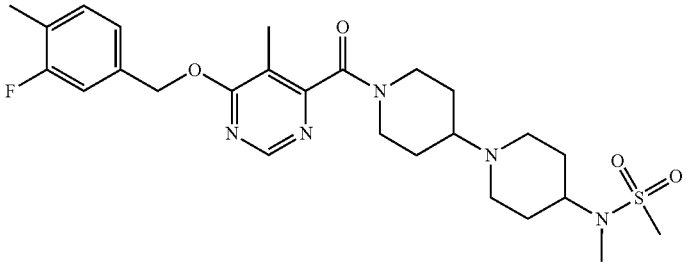
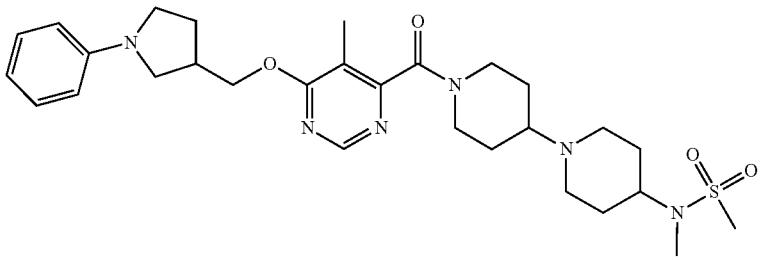
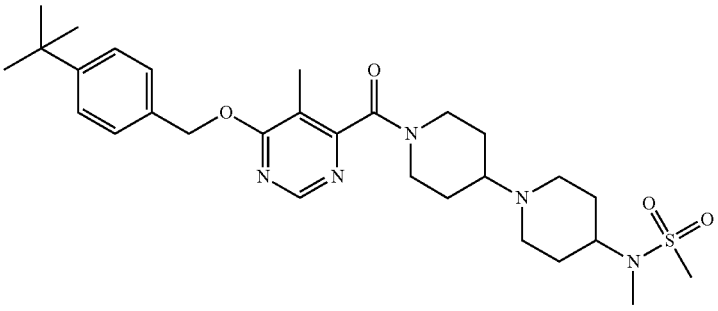
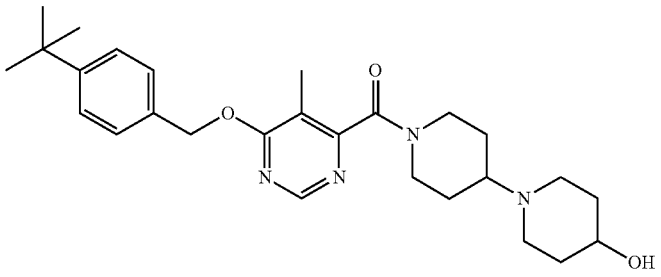


Sodium hydride (19 mg, 0.46 mmol) and 4-chloro-3-methylbenzylalcohol (44 mg, 0.28 mmol) were suspended in 5 ml of dry tetrahydrofuran. The reaction mixture was stirred at room temperature for 10 min, then Intermediate 25b (100 mg, 0.23 mmol) was added. The reaction mixture was stirred at 50° C. overnight. The solvent was concentrated under vacuum, the crude product was dissolved in dichloromethane and the organic phase was washed with water, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Si Isolute cartridge (5 g); eluent: dichloromethane/methanol=95/5%). 40 mg (0.07 mmol) of the desired product were obtained.

HPLC (Method 1E Hydro): R_t. (min)=9.95

$[M+H]^+$=550

The following examples were synthesized in analogy to the preparation of Example 292.

Ex #	STRUCTURE	Inter-mediate	Phenol	[M + H]$^+$	HPLC R_t (min)	Meth-od
293		25b	4-hydroxy-methyl-benzo-nitrile	527	8.17	1E (Hy-dro)
294		25b	(3-fluoro-4-methyl-phenyl)-methanol	534	9.12	1E (Hy-dro)
295		25b	(1-phenyl-pyrrolydin-3-yl)-methanol	571	10.2	1E (Hy-dro)
296		25b	(4-tert-butyl-phenyl)-methanol	558	2.71	1F
297		25f	(4-tert-butyl-phenyl)-methanol	466	9.50	1E (Hy-dro)

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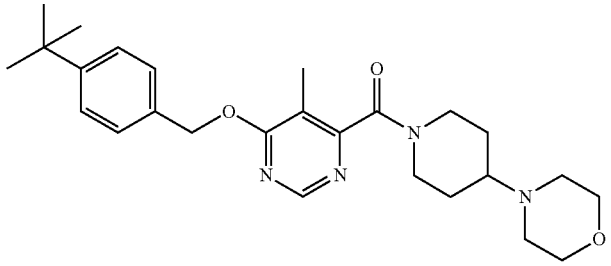
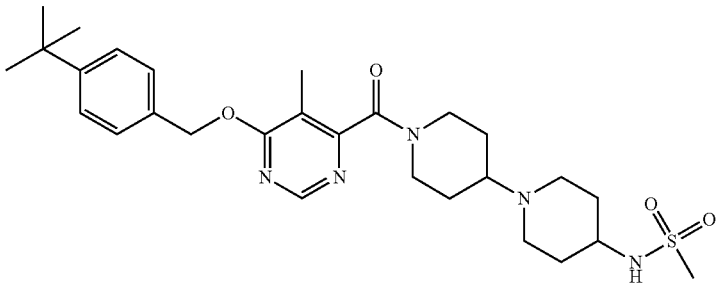
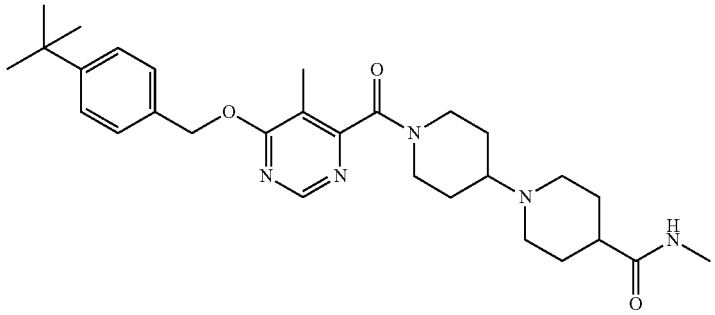
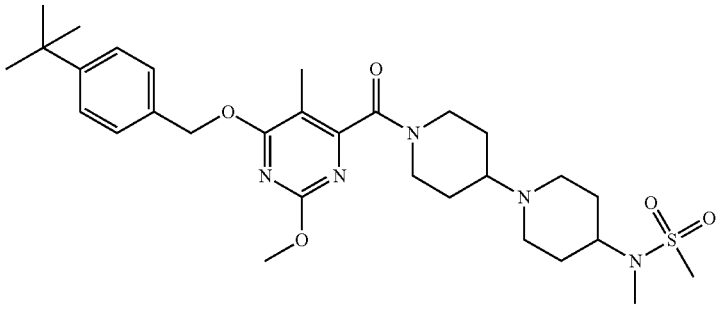
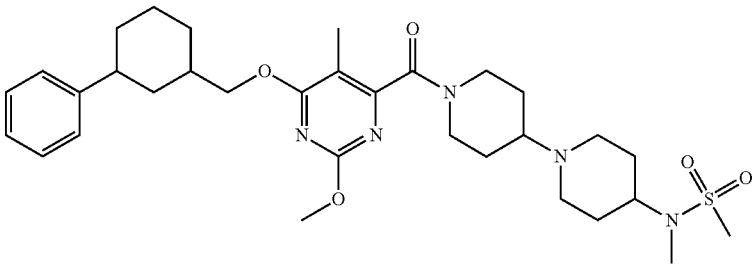
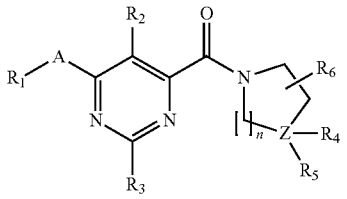
Ex #	STRUCTURE	Inter-mediate	Phenol	[M + H]+	HPLC R_t (min)	Meth-od
298		25h	(4-tert-butyl-phenyl)-methanol	453	8.01	2F
299		25a	(4-tert-butyl-phenyl)-methanol	544	9.68	1E (Hy-dro)
300		25d	(4-tert-butyl-phenyl)-methanol	508	10.25	1E (Hy-dro)
301		25n	(4-tert-butyl-phenyl)-methanol	588	2.20	2Ca
302		25n	(3-Phenyl-cyclo-hexyl)-methanol	614	2.18	2Ca

The invention claimed is:

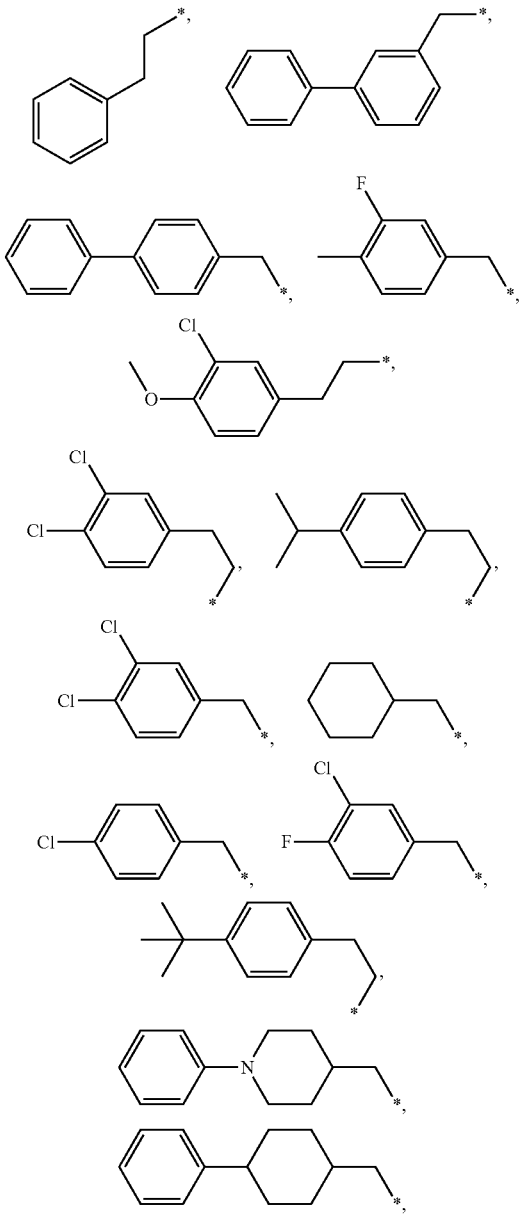
1. A process for the production of a compound of formula (I),



(I)

wherein

R_1 is selected from the group consisting of



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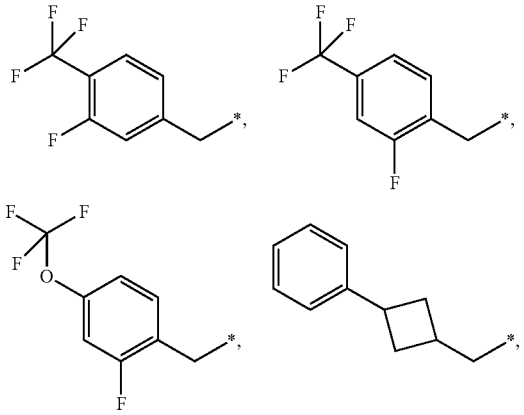

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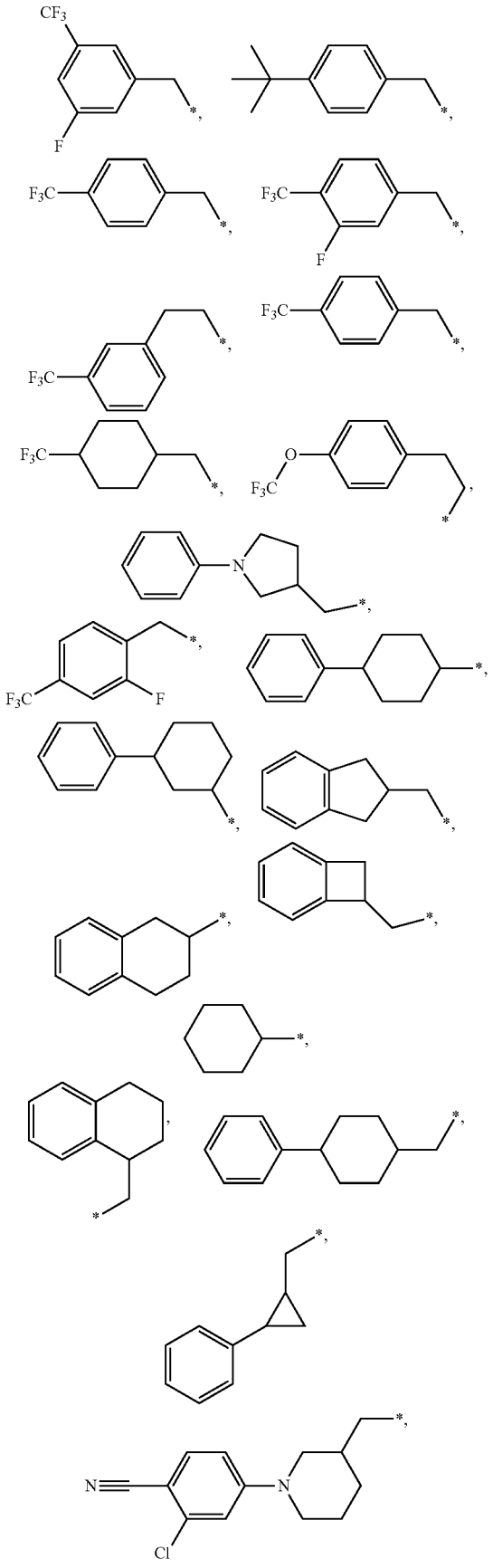

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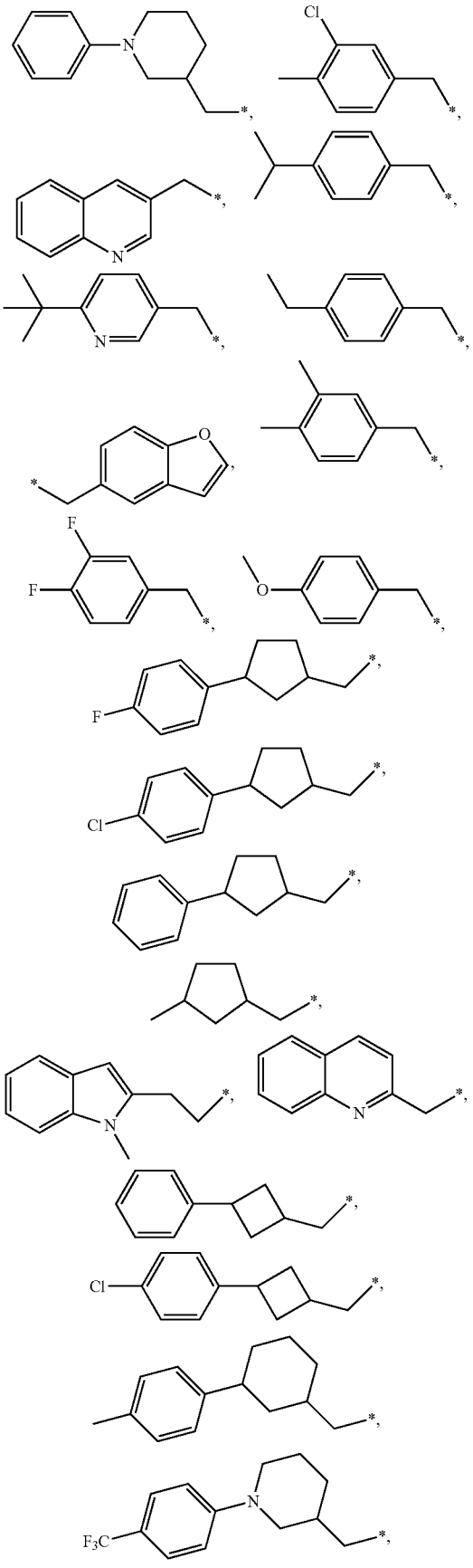

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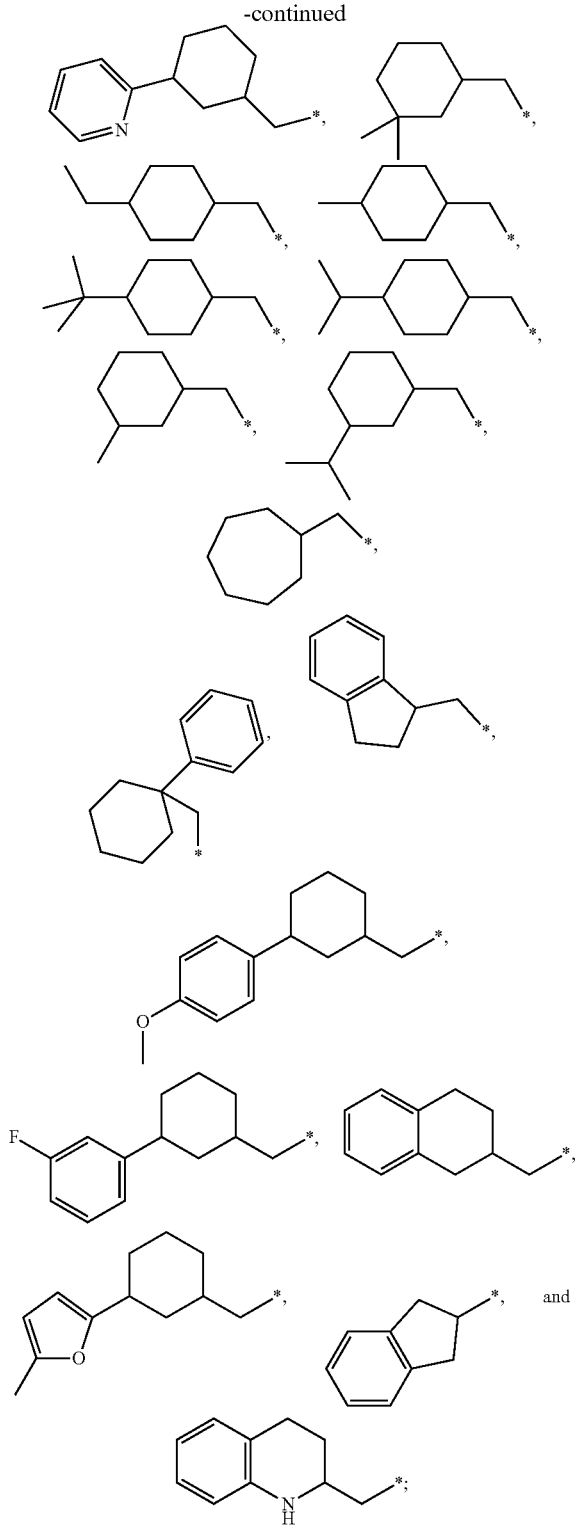


R_2 is selected from the group consisting of —H, -halogen, —CN, —O—C_1-C_4-alkyl, —C_1-C_4-alkyl, —CH═CH_2, —C≡CH, —CF_3, —OCF_3, —OCF_2H, and —$OCFH_2$;

R_3 is selected from the group consisting of —H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, —OCH_3, and —CN;

R_4 and R_5 are independently selected from the group consisting of an electron pair, —H, —C_1-C_6-alkyl, —NH_2, —C_3-C_8-cycloalkyl, —C_3-C_8-heterocyclyl, —C_5-C_{10}-aryl, —C_5-C_{10}-heteroaryl, and —C(O)—$N(R_8,R_{8'})$, with R_8 and $R_{8'}$ independently being selected from the group consisting of —H, and —C_1-C_6-alkyl,

and wherein R_4 and R_5 if different from an electron pair or —H are optionally independently substituted with one or more groups selected from the group consisting of -halogen, —OH, —CF_3, —CN, —C_1-C_6-alkyl, —O—C_1-C_6-alkyl, —O—C_3-C_8-cycloalkyl, —O—C_3-C_8-heterocyclyl, —O—C_5-C_{10}-aryl, —O—C_5-C_{10}-heteroaryl, —C_0-C_6-alkylene-CN, —C_0-C_4-alkylene-O—C_1-C_4-alkyl, —C_0-C_4-alkylene-O—C_3-C_8-cycloalkyl, —C_0-C_4-alkylene-O—C_3-C_8-heterocyclyl, —C_0-C_4-alkylene-O—C_5-C_{10}-aryl, —C_0-C_4-alkylene-O—C_5-C_{10}-heteroaryl, —C_0-C_4-alkylene-Q-C_0-C_4-alkyl-$N(R_9,R_{9'})$, —C_0-C_4-alkylene-$N(R_{10})$-Q-C_1-C_4-alkyl, —C_0-C_4-alkylene-$N(R_{10})$-Q-C_3-C_8-cycloalkyl, —C_0-C_4-alkylene-$N(R_{10})$-Q-C_3-C_8-heterocyclyl, —C_0-C_4-alkylene-$N(R_{10})$-Q-C_5-C_{10}-aryl, —C_0-C_4-alkylene-$N(R_{10})$-Q-C_5-C_{10}-heteroaryl, —C_0-C_4-alkylene-Q-$N(R_{11},R_{11'})$, —C_0-C_4-alkylen-$N(R_{12})$-Q-$N(R_{13},R_{13'})$, —C_0-C_4-alkylen-R_{14}, —C_0-C_4-alkylene-Q-C_1-C_6-alkyl, —C_0-C_4-alkylene-Q-C_3-C_8-cycloalkyl, —C_0-C_4-alkylene-Q-C_3-C_8-heterocyclyl, —C_0-C_4-alkylene-Q-C_5-C_{10}-aryl, —C_0-C_4-alkylene-Q-C_5-C_{10}-heteroaryl, —C_0-C_4-alkylene-O-Q-$N(R_{15},R_{15'})$, and —C_0-C_4-alkylene-$N(R_{16})$-Q-O—(R_{17}),

wherein Q is —C(O)— or —SO_2—,

wherein R_{12}, R_{16}, are independently selected from the group consisting of —H, —C_1-C_6-alkyl, and —C_3-C_6-cycloalkyl,

wherein R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$, R_{13}, $R_{13'}$, R_{15}, $R_{15'}$, are independently selected from the group consisting of —H, —C_1-C_6-alkyl, and —C_3-C_6-cycloalkyl,

or wherein R_9 and $R_{9'}$, R_{11} and $R_{11'}$, R_{13} and $R_{13'}$, R_{15} and $R_{15'}$ together form a —C_2-C_6-alkylene group,

wherein R_{14} and R_{17} are independently selected from the group consisting of —H, —C_1-C_6-alkyl, —C_5-C_{10}-aryl, —C_5-C_{10}-heteroaryl, —C_3-C_8-cycloalkyl, and —C_3-C_8-heterocyclyl, wherein said —C_3-C_8-heterocyclyl optionally comprises nitrogen and/or —SO_2— in the ring,

and wherein R_{14} and R_{17} are optionally substituted with one or more groups selected from the group consisting of —OH, —OCH_3, —CF_3, —OCF_3, —CN, -halogen, —C_1-C_4-alkyl, ═O, and —SO_2—C_1-C_4-alkyl,

or R_4 and/or R_5 are independently a group of the structure -L_2-R_{18},

wherein L_2 is —NH— and/or $N(C_1$-C_4-alkyl)-,

wherein R_{18} is —C_5-C_{10}-aryl, —C_5-C_{10}-heteroaryl, —C_3-C_8-cycloalkyl or —C_3-C_8-heterocyclyl,

wherein R_{18} is optionally substituted by one or more groups selected from the group consisting of halogen, —CF_3, —OCF_3, —CN, —OH, —O—C_1-C_4-alkyl, —C_1-C_6-alkyl, —NH—C(O)—C_1-C_6-alkyl, —$N(C_1$-C_4-alkyl)-C(O)—C_1-C_6-alkyl, —C(O)—C_1-C_6-alkyl, —$S(O)_2$—C_1-C_6-alkyl, —NH—$S(O)_2$—C_1-C_6-alkyl, —$N(C_1$-C_4-alkyl)-$S(O)_2$—C_1-C_6-alkyl, and —C(O)—O—C_1-C_6-alkyl;

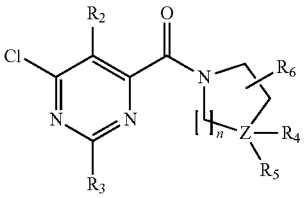
R_6 is selected from the group consisting of —H, —C_1-C_4-alkyl, —OH, —O—C_1-C_4-alkyl, -halogen, —CN, —CF_3, and —OCF_3;

A is —NH—;

n is 1, 2 or 3;

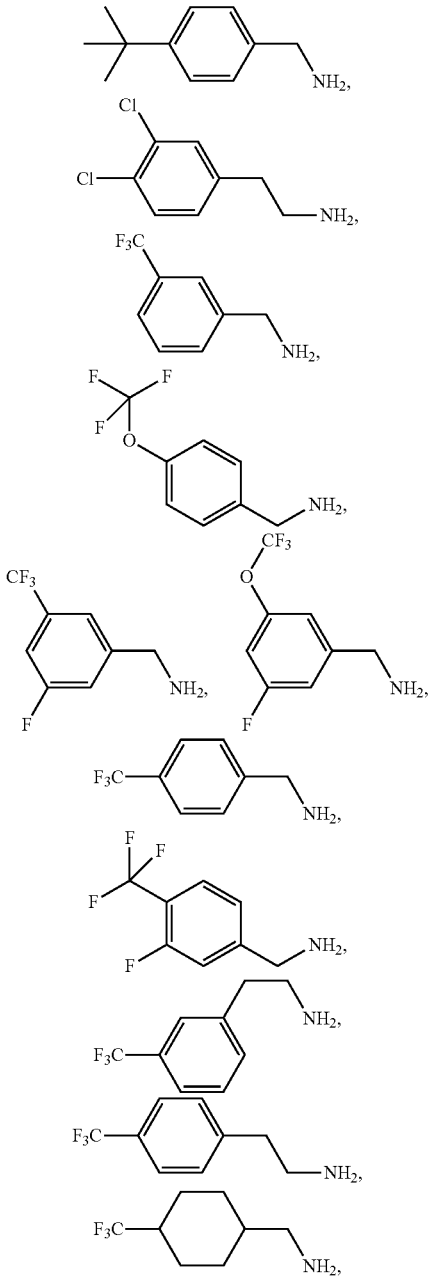
Z is C or N,

characterized in that a compound of formula II



(II)

in which R_2, R_3, R_4, R_5, R_6, Z, and n have the meaning as in formula I, is coupled with a primary amine selected from the group consisting of



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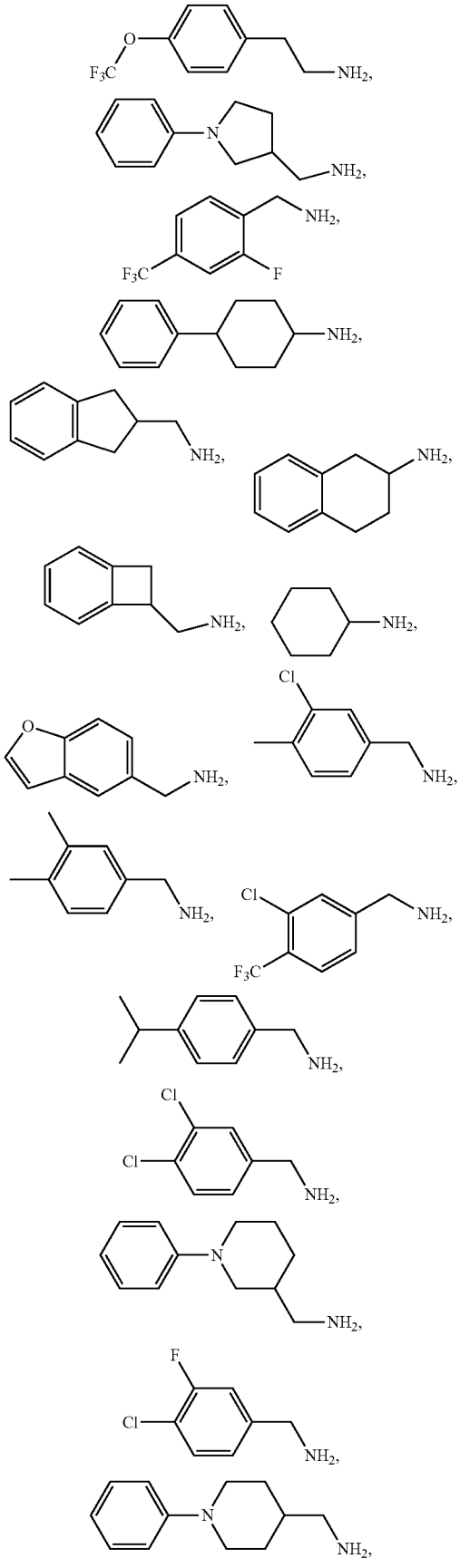

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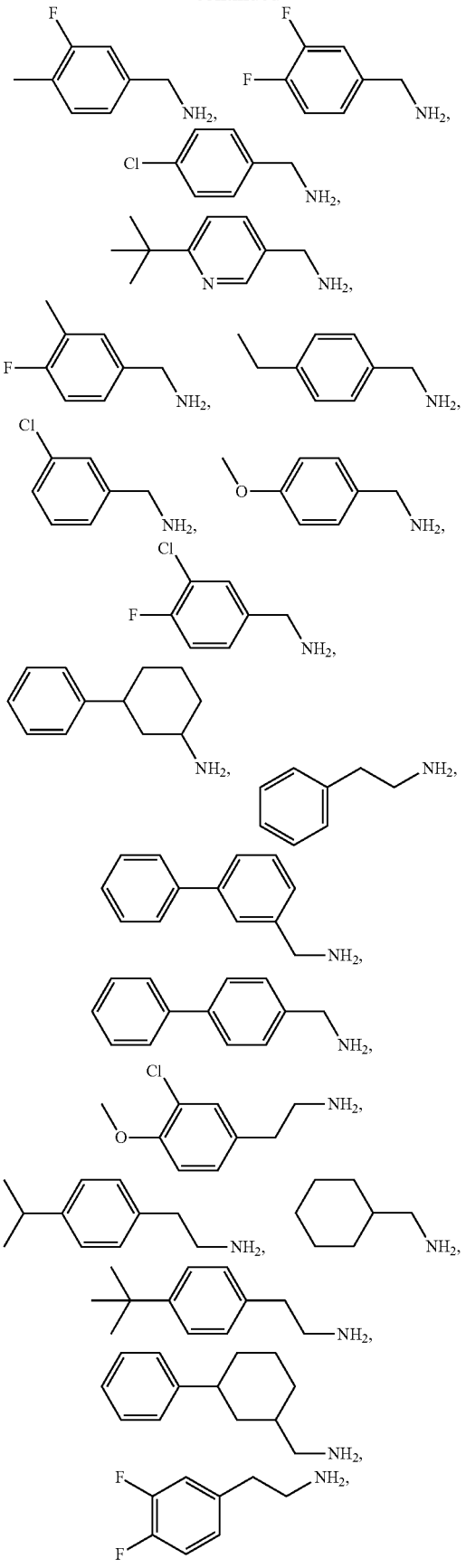

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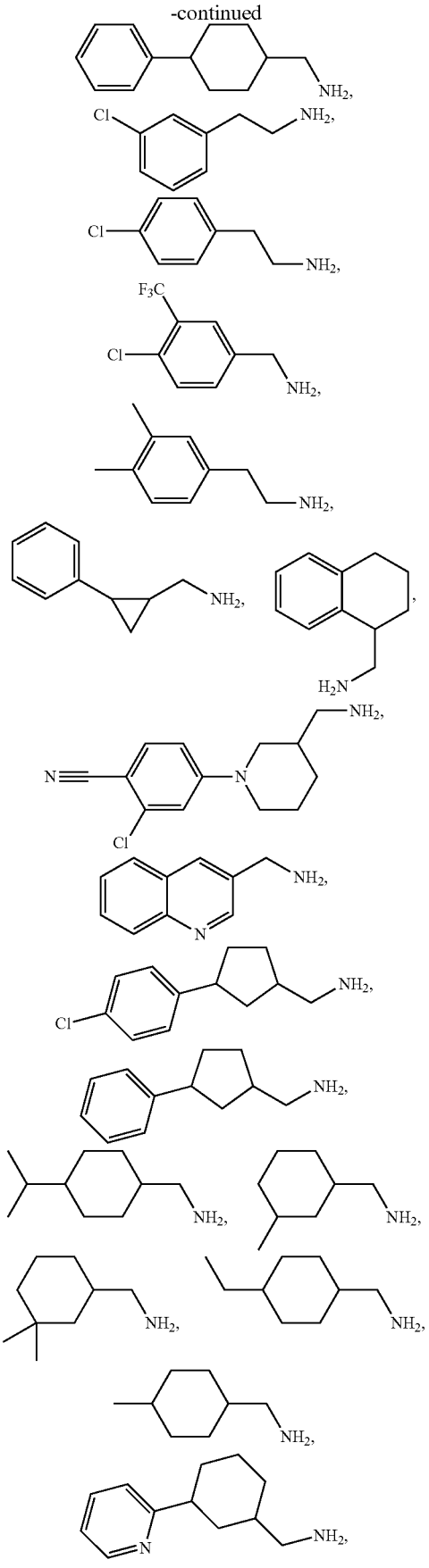

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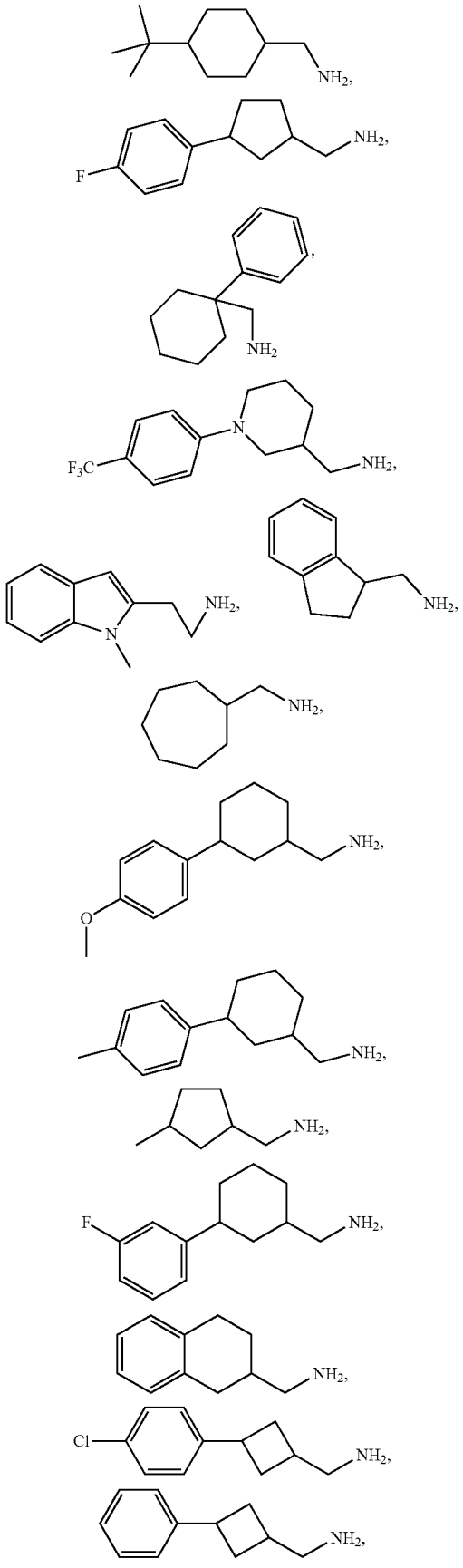

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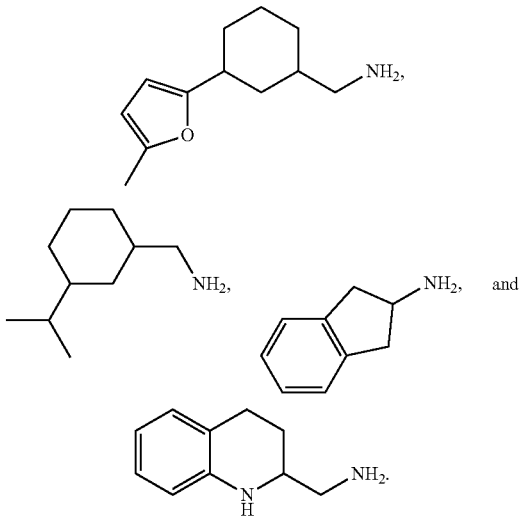


and

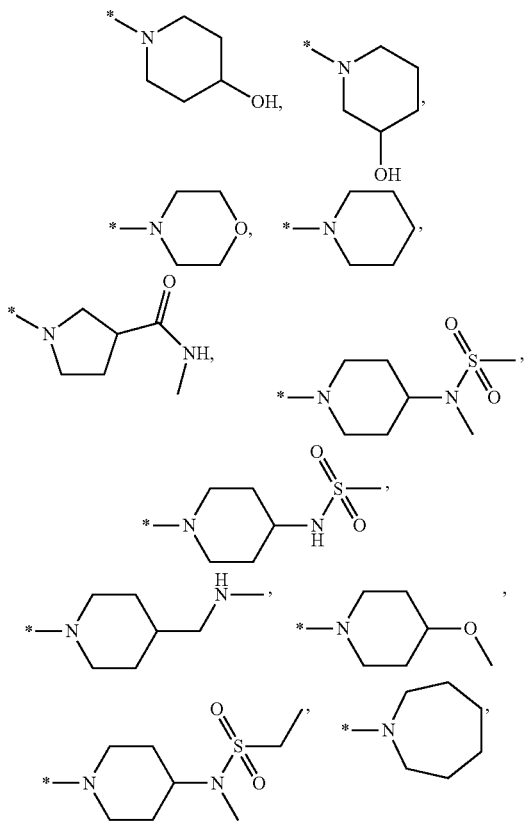
2. The process for the production of the compound of formula (I) according to claim **1**,

wherein

R_2 is selected from the group consisting of —H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, -butyl, -i-butyl, -t-butyl, —F, —Cl, —Br, —I, —CN, —CH═CH_2, —CCH, and —OCH_3;

R_3 is —H, -methyl, and/or —OCH_3;

R_4 is selected from the group consisting of



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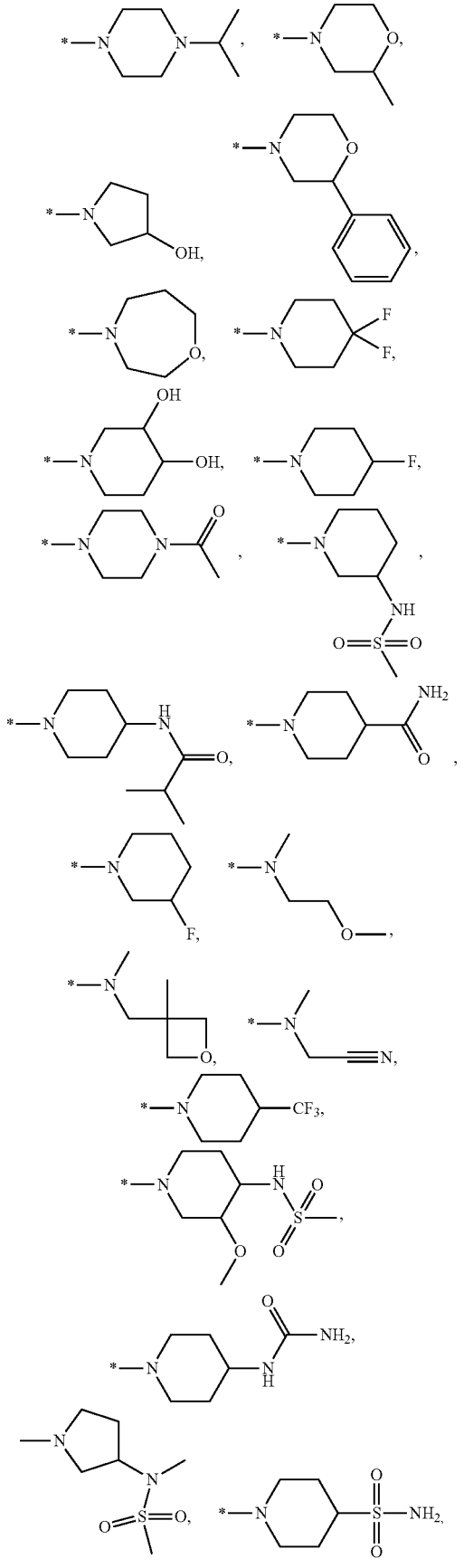

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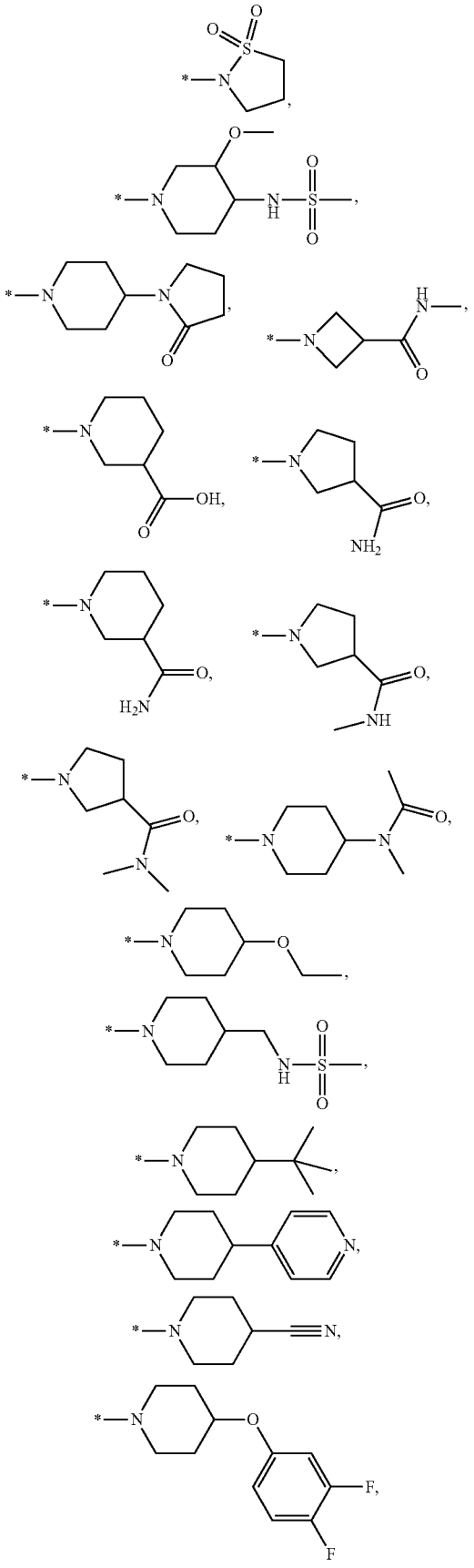

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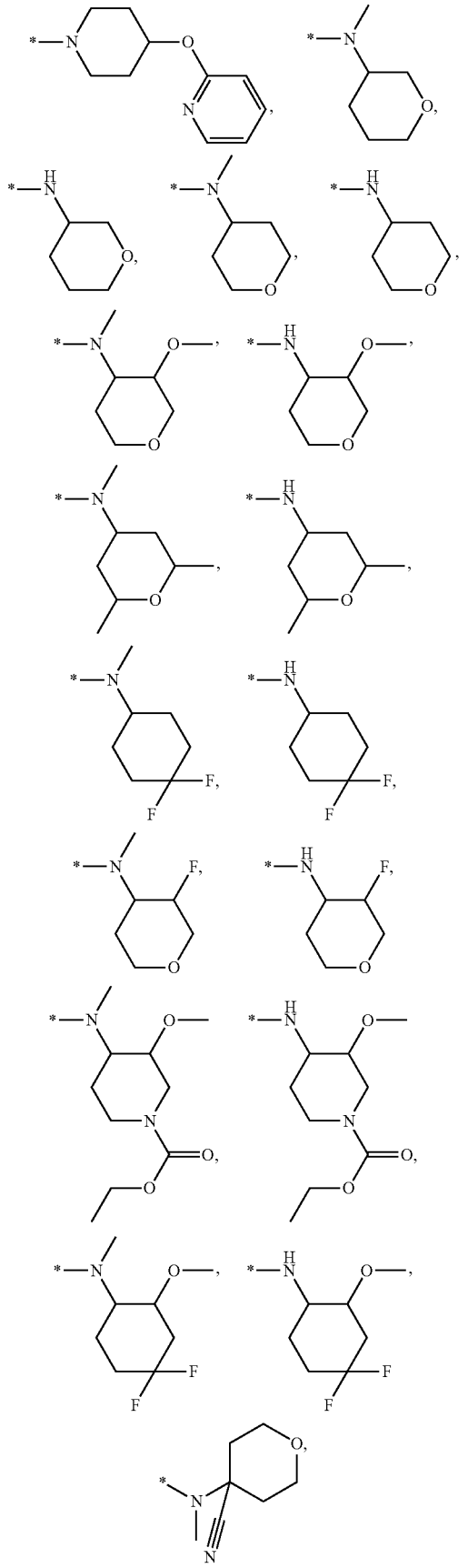

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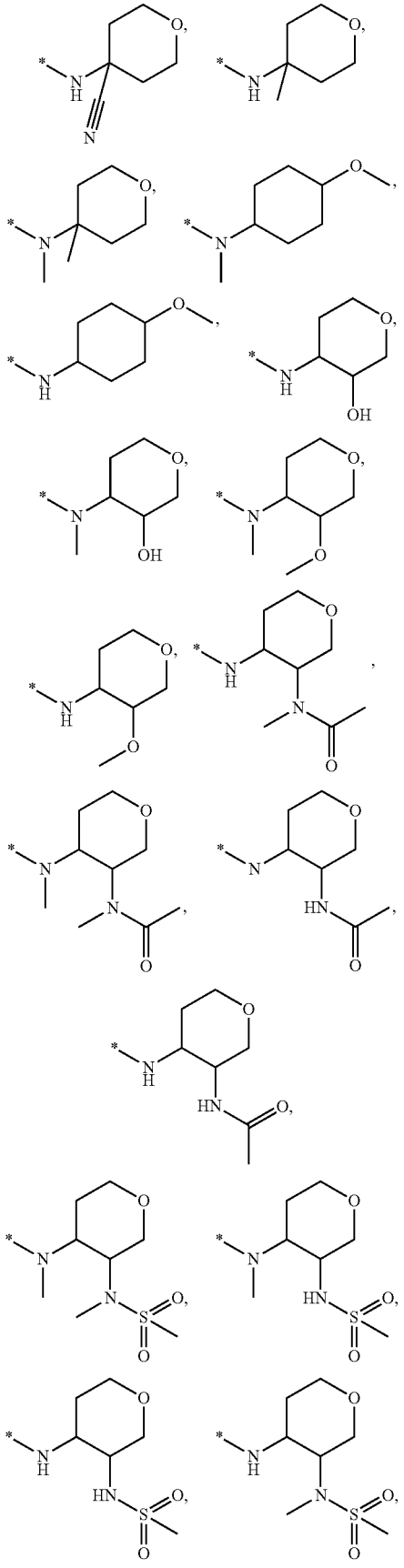

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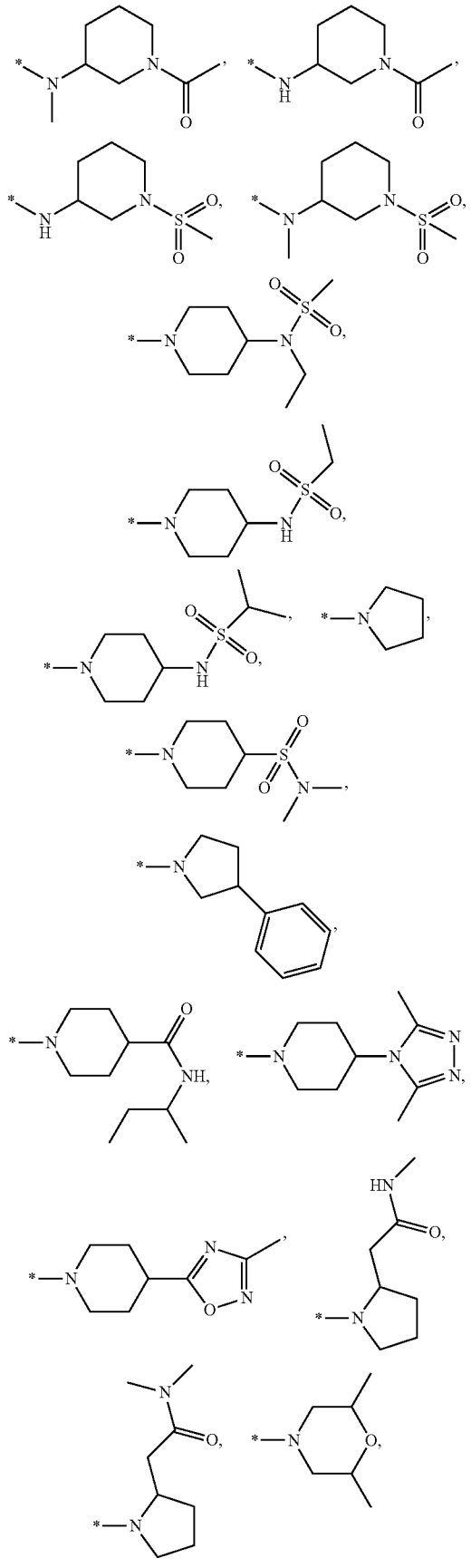

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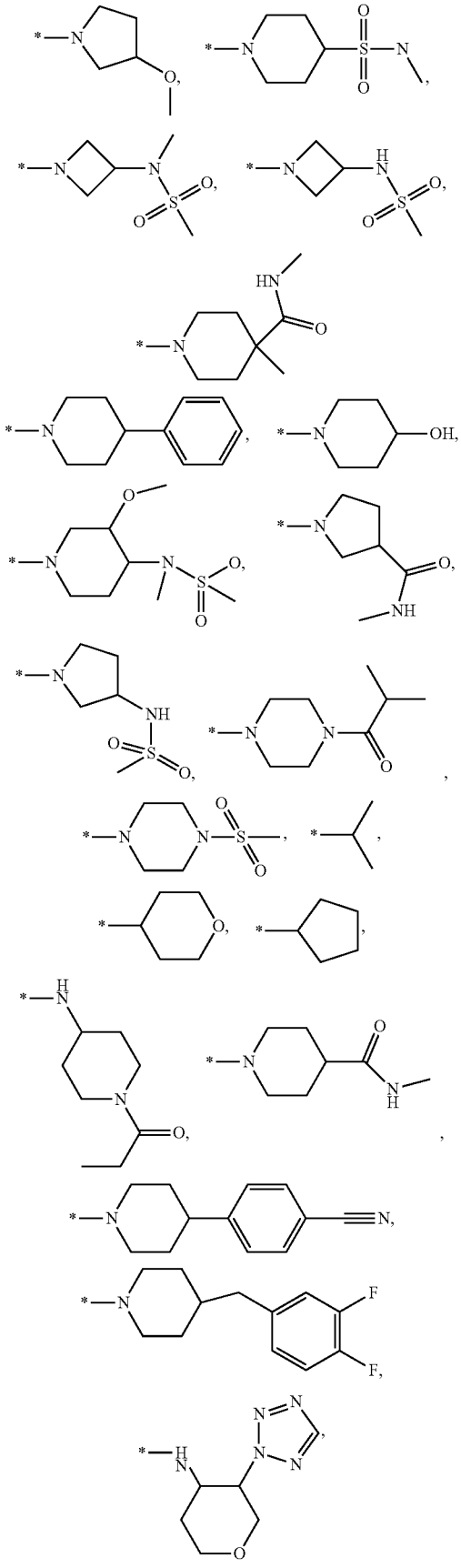

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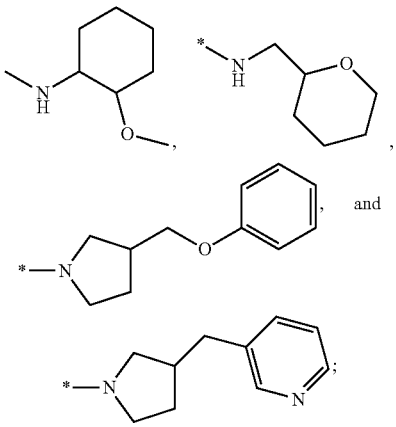


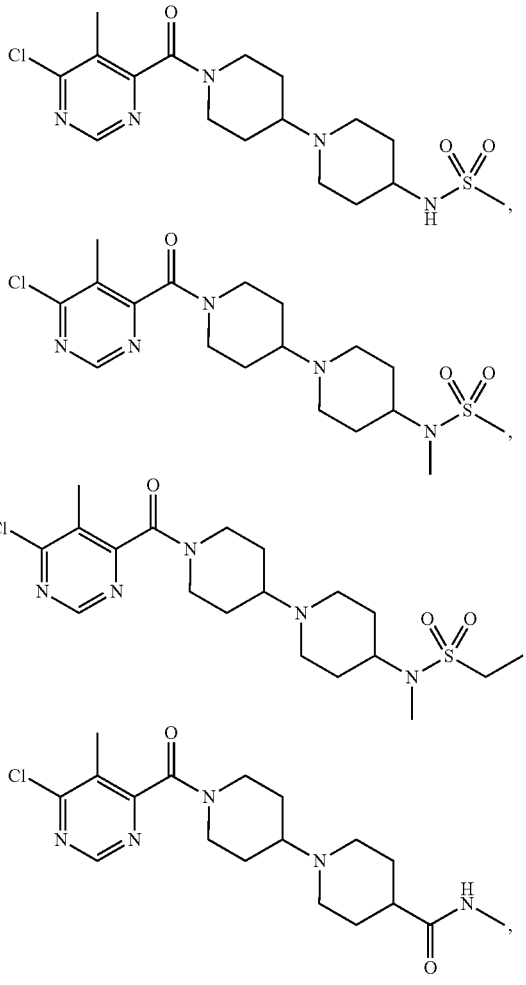
and

R_5 is —H or —C(O)—NH_2;

R_6 is selected from the group consisting of —H, —CH_3, —C_2H_5, —O—CH_3, —O—C_2H_5, —F, —CF_3, and —OCF_3; and

Z is C.

3. An intermediate compound selected from the group consisting of



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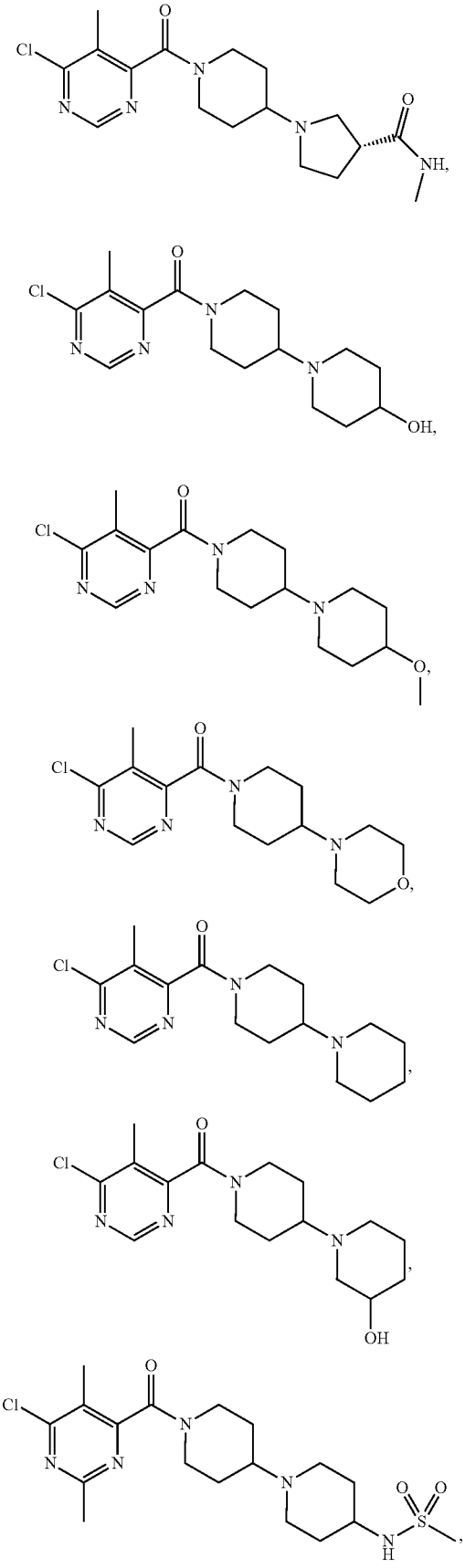

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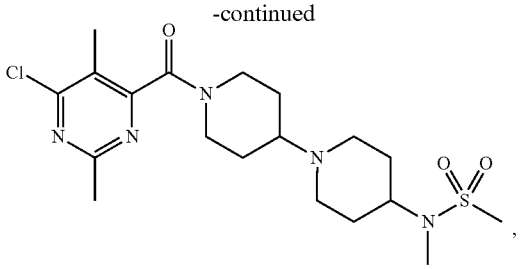
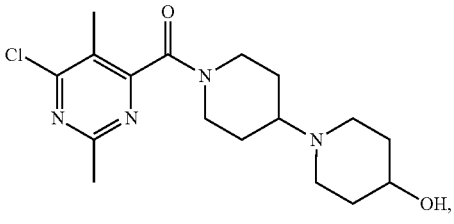
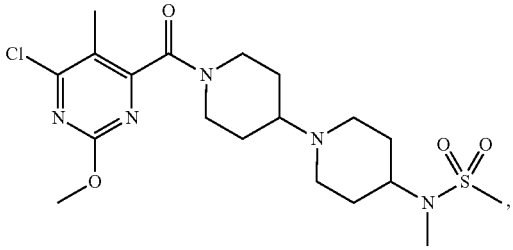
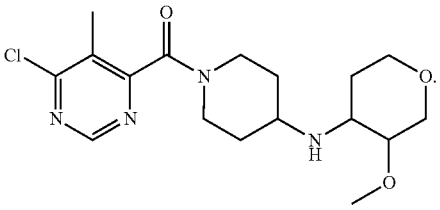


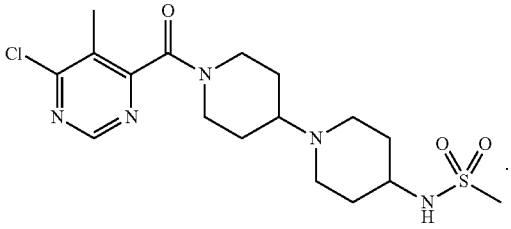




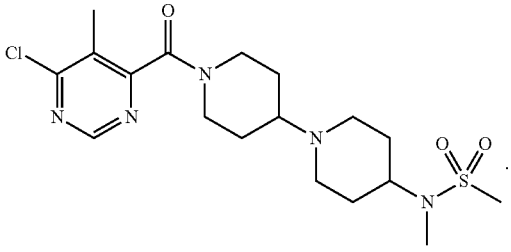
and



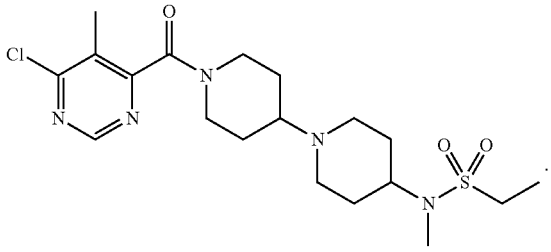
4. The intermediate according to claim **3**, wherein the intermediate is



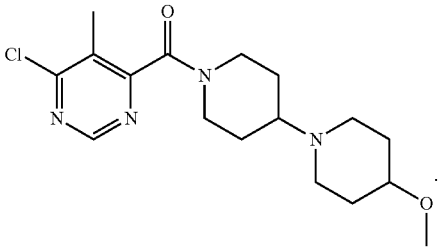
5. The intermediate according to claim **3**, wherein the intermediate is



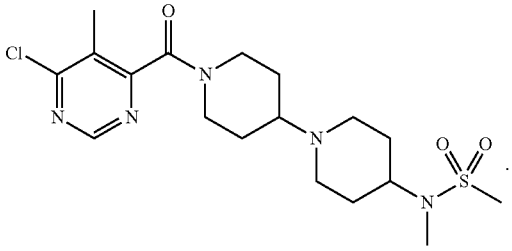
6. The intermediate according to claim **3**, wherein the intermediate is



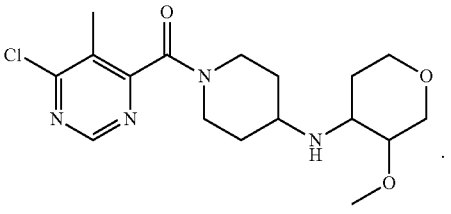
7. The intermediate according to claim **3**, wherein the intermediate is



8. The intermediate according to claim **3**, wherein the intermediate is



9. The intermediate according to claim **3**, wherein the intermediate is



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